International Journal Dental and Medical Sciences Research
Volume 3, Issue 1, Jan-Feb 2021 pp 1120-1124 www.ijdmsrjournal.com ISSN: 2582-6018

Familial Hypercholesterolemia - A Tale of Two Siblings

Shikha Verma[1], Seema Sharma[2], Ravinder Singh[3]
[1,3]*Senior resident, MD*
[2] *Associate Professor,MD*
[1,2,]*Department of Pediatrics,Dr Rajendra Prasad Government Medical College, Kangra at Tanda , Himacal Pradesh, India*
[3]*Department of Dermatology, Dr Rajendra Prasad Government Medical College, Kangra at at Tanda , Himacal Pradesh, India*

Submitted: 10-02-2021 Revised: 20-02-2021 Accepted: 25-02-2021

ABSTRACT: Familial hypercholesterolemia is a rare autosomal co-dominant monogenic disease resulting into genetic dyslipidaemia. It is characterized by an increase in serum LDL cholesterol concentrations, presence of xanthomas and premature atherosclerosis.In that the individuals with two mutant LDL receptor alleles (FH Homozygotes) are much more affected than those with one mutant allele (FH Heterozygotes).FH in Homozygous state is rare and occurs in approximately1 in 1 million persons. These patients are at a high risk of developing coronary heart disease and sudden death, unless the condition isrecognized and treated promptly. Here we report an interesting pair of siblings with HoFH for its academic interest along with a brief review of literature.

KEY WORDS: Cholesterol, Coronary artery disease

I. INTRODUCTION:

Familial hypercholesterolemia (FH) is an autosomal dominant hereditary disease in which mutations occur in the low-density lipoprotein (LDL) receptor and its related genes that results in reduced uptake and clearance of LDL-c. Individuals with two mutated LDL receptor alleles are known as Homozygous FH and one mutated allele as Heterozygous FH. The frequency of homozygous FH (HoFH) is estimated as 1 in 1,000,000, and that of heterozygous FH (HeFH) as 1 in 500, but more recent reports showed higher prevalence of 1:100–250[1]. Increased serum cholesterol produces several clinical manifestations, including xanthomas, xanthelasma, corneal arcus, aortic valve disease and premature coronary artery disease (CAD)[2] .There are potentially as many as 4.5 million individuals in Europe with HeFH and possibly 35 million around the world, of whom 20–25% of these are children and adolescents. Given the high prevalence of FH, it is estimated that one baby is born with FH every minute. However, FH is very much under diagnosed and undertreated globally. Children with FH have higher risk of early coronary events and death from myocardial infarction due to premature atherosclerosis[3]. In order to reduce the risk of atherosclerotic cardio vascular disease (ASCVD) in patients with HoFH, it is important to correctly diagnose patients as early as possible and provide aggressive interventions to reduce the cumulative LDL-C burden[4]. These patients are managed with life style modification, lipid lowering drugs, if not responded then LDL apheresis and liver transplantation[2]. In general, patients with HoFH do not survive beyond 30 years without therapeutic interventions[5].

Here we report an interesting pair of siblings with HoFH for its academic interest along with a brief review of literature.

CASE REPORT 1 : A 10 year female adolescent born to non consanguineous parents presented with complaints of multiple swellings on dorsum of both hands and bilateral elbow joints for last one year which were progressive in nature, painless ,non itchy with no history of joint pain. There was no history of chest pain, breathlessness, hypertension, diabetes mellitus, hypothyroidism or any other chronic illness and she was not on any medications. In the family history there were similar complaints in the younger brother since three years . On examination vital signs were normal without jaundice ,anemia, pedal edema,clubbing and cyanosis. No carotid artery bruit was present. Anthropemetric assessment showed height 129.5cm, weight 20.8 kg and BMI of 12.4 kg/m^2. Dermatological examination revealed multiple tendinous xanthomas of varying sizes over bilateral metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalageal (DIP) joints and tuberous xanthomas over bilateral elbows. Cutaneous intertriginous xanthomas were present over natal cleft (figure1). Rest of systemic examination was normal . On investigations her haematological parameters,

International Journal Dental and Medical Sciences Research
Volume 3, Issue 1, Jan-Feb 2021 pp 1120-1124 www.ijdmsrjournal.com ISSN: 2582-6018

renal, liver and thyroid function tests were within normal limits. Lipid profile showed increased total cholesterol (679mg/dl), LDL cholesterol (630mg/dl) with normal triglyceride levels (135mg/dl) (Table1). Echocardiography showed mild AR with good left ventricular function. Carotid doppler for carotid intimal media thikness (CIMT) was normal. Based on above findings, a homozygous familial hypercholesterolemia was considered.

CASE REPORT 2: A 8 year male child, younger brother of index case presented with complaints of yellowish swellings over bilateral elbow joints for last three years.

General physical examination was within normal limit with anthropometry of height 123.5cm, weight18.7 kg and BMI of 12.2 kg/m^2. Dermatological examination revealed tuberous xanthomas over bilateral elbows . Dorsum of the hands showed characteristic involvement of interdigital space showing the pathognomonic intertriginous xanthoma. Bilateral corneal arcus was also present (figure2).On investigations his hematological parameters, renal, liver and thyroid function tests were within normal limits. Lipid profile of the patient showed increased total cholesterol (592mg/dl), LDL cholesterol (551mg/dl) with normal triglyceride levels (115mg/dl). Echocardiography showed mild AR with good left ventricular function. Carotid doppler for CIMT was normal. Lipid profile of mother of the children was also done and found to be abnormal (Table 2).

The diagnosis of homozygous FH in our patients was based on the following:-

1. Serum cholesterol levels [500 mg/dl ([12 mmol/dl)with normal triglyceride levels
2. Appearance of xanthomas in the first decade of life
3. Documentation of hypercholesterolemia in mother and in both siblings
4. The presence of rare pathognomonic intertriginous xanthomas, which have been described as a marker of this homozygous type

Due to financial constraints LDL receptor studies and genetic analysis could not be done in our patients. They were advised life style modification, treated with statins (atorvastatin 20 mg OD) and advised for follow up. Their lipid profile after 6 months showed no decrease in total and LDL cholesterol.

II. DISCUSSION:

Familial hypercholesterolemia is caused by a mutation in the LDL-receptor gene. If a mother or father has HeFH, there is a 50% probability that the child will also have HeFH. If both parents have HeFH, then the child has a 25% probability of having HoFH and a 50% chance of having HeFH. The genetic mutations underlying FH affect the production and processing of cell surface LDL receptors resulting in impaired hepatic clearance of circulating LDL particles, which leads to their accumulation in bloodstream[6]. HoFH results from two mutated genes which in turn compromises clearance of LDL-C through the low-density lipoprotein receptor (LDL-R).FH is characterized by life-long elevated plasma LDL cholesterol (LDL-C) levels, presence of tendon xanthomas, and increased risk of premature atherosclerotic cardiovascular disease (ASCVD) (Table 2)[7]. With sustained exposure of the arterial wall to elevated LDL-C levels, atherosclerosis develops, especially in the coronary arteries. Therefore, early diagnosis and optimal treatment from childhood are critical in preventing premature ASCVD in children and adolescents with FH[8].

The patients with HoFH often present with the development of xanthomatosis before the first decade of life. Patients have multiple types of xanthomata,which include tuberous, sub periosteal, tendon xanthomas, elevated xanthomatous plaques and the rare but characteristic intertriginous xanthomas [9]. Xanthoma (from Greek—yellow) are plaques or nodules consisting of abnormal lipid deposition in foam cells (macrophages with phagocytosed lipid material) and collagen which develop because of lipid leakage from the vessels into the surrounding tissue, where macrophages subsequently phagocytose these lipids. As the cholesterol is not degraded, it accumulates within these cells, creating ‘‘foamy’’ macrophages. The extracellular cholesterol crystallizes into clefts and induces an inflammatory reaction with giant cells and resultant fibrosis . On the contrary, the heterozygous FH subjects are usually asymptomatic with no abnormal physical findings, and are usually detected in adolescent period with elevated LDL levels prompted by a family history of premature CAD or dyslipidemia. In the primary care setting, the diagnosis of FH may be easily missed. Patients are commonly identified after experiencing a cardiovascular event at an unexpected age or as a result of a family member being diagnosed.

HoFH is likely when LDL-C levels are greater than 13 mmol/L (500 mg/dL) in adults and 11 mmol/L (420 mg/dL) in children [10]. Triglyceride (TG) levels may remain normal . HoFH patients usually have a worse prognosis, succumbing to complications by the second decade. In addition to

cholesterol levels, diagnosis may be supported by features seen during physical examination such as tendonxanthomas on the dorsal aspect of the metacarpophalangeal joints or at the calcaneal tendon, and corneal arcus.FH can result into severe myocardial infarction ,often leading to sudden death takes place during the third to fifth decades of life. Hence early diagnosis, dietary modifications and drug therapy with statins and bile acid sequestrants is very important in these patients [11] . But drug therapy has been found to be less efficacious and unresponsive in homozygous FH compared to heterozygous patients in whom other treatment modalities like liver transplantation, LDL apheresis and portacaval shunting may have to be considered as extreme options.

This case study highlights that despite huge medical advancement FH remains seriously under-diagnosed, with a delay in the treatment. With early diagnosis and prompt treatment these patients can live longer and more productive lives. The diagnosis of FH is important not only for the prognosis of the patient but also has implications for the family members who may have inherited the same disorder. Therefore genetic counselling and screening of first degree relatives and extended family members plays an important role in early detection and treatment. Awareness on this disorder is somehow lacking even among the clinicians . Early detection will allow immediate lipid-lowering medications to be commenced to reduce the risk of progression to CAD. Children diagnosed with FH require commencement of statin treatment as early as 8 to 10 years old. Treatment with statin should be started with low doses and then increased to achieve the treatment goals. The goal in children above 10 years of age is LCL-c < 3.5mmol/L whereas a level of atleast a 50% reduction in the LDL-c level for younger children[12] .

III. CONCLUSION:

Clinical identification of Xanthomas and knowledge of their association with CAD is essential for every physician as early diagnosis and early treatment can prevent premature deaths due to CAD. All the family members should be screened for dyslipidemia.

Legends

Figure1: Case 1
(A) Bilateral Corneal Arcus
(B) Tendinous xanthomas over MCP, PIP& DIP joints
(C) Tuberous xanthomas over elbows
(D) Intertriginous xanthomas over the natal cleft
Figure 2: Case 2
(A) Bilateral Corneal Arcus
(B) Intertriginous xanthomas inter-digital area
(C,D) Tuberous xanthomas over elbows

Table 1: Lipid Profile of The Family
Table 2: European Atherosclerosis Society Diagnostic Criteria For Homozygous Familial Hypercholesterolemia

Financial disclosure statement: The authors have no financial relationships relevant to this article to disclose.
Funding source: None
Conflict of interest statement: The authors have no conflicts of interest relevant to this article to disclose

Contributors' Statement

SV ,SS and RS conceptualized the perspective, drafted the manuscript . SS and SV reviewed and revised the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

REFERENCES:

[1]. Vallejo-Vaz AJ, De Marco M, Stevens CAT, Akram A, Freiberger T, Hovingh GK, et al. Overview of the current status of familial hypercholesterolaemia care in over 60 countries - the EAS familial hypercholesterolaemia studiescollaboration (FHSC). Atherosclerosis. 2018;277:234–55.
[2]. Rader D J, Hobbs HH. Disorders of lipoprotein metabolism. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al editors. Harrison Principles of Internal Medicine. 17th ed, Vol.2, New York: Mc Graw Hill Inc; 2008.p.2416-429.
[3]. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M.Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36:2425–37.
[4]. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia:new insights and guidance for clinicians to improve detection and clinicalmanagement. A position paper from the Consensus Panel on FamilialHypercholesterolaemia of the European Atherosclerosis Society.
[5]. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial

hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol. 2004;160:407–20.
[6]. Al-Shaikh AM, Abdullah MH, Barclay A, Cullen-DeanG, McCrindle BW. Impact of the characteristics ofpatients and their clinical management on outcomes inchildren with homozygous familialhypercholesterolemia. Cardiol Young 2002; 12:105–12.
[7]. Benn M, Watts GF, Tybjaerg-Hansen A,Nordestgaard BG. Familial hypercholesterolemiain the danish general population: prevalence,coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012;97:3956–64.
[8]. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia:new insights and guidance for clinicians to improve detection and clinicalmanagement. A position paper from the Consensus Panel on FamilialHypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J2014;35:2146–57
[9]. White LE. Xanthomatoses and lipoprotein disorders. In: Klaus Wolff LAG, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, editors.Fitzpatrick's dermatology in general medicine. 7th ed. New York: McGraw-Hill; 2008. p. 1272.
[10]. In: Identification and management of familialhypercholesterolaemia (FH). London; 2008.
[11]. Fahed AC, Nemer GM. Familial hypercholesterolemia: the lipidsor the genes? Nutr Metab (Lond). 2011;8:23.
[12]. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H,Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the EuropeanAssocciation for Cardiovascular Prevention & Rehabilitation (EACPR).Atherosclerosis. 2016;253:281–344.

Table I- Lipid Profile of The Family

Family member	Totalcholesterol(TC)	Triglyceride(TG)	LDL
Index	679	135	630
Brother	592	115	551
Mother	270	140	190

Table-II European Atherosclerosis Society Diagnostic Criteria For Homozygous Familial Hypercholesterolemia[19]

(a)	Two mutant alleles at the LDLR,ApoB,PCSK9,orLDLRAP1 genelocus
(b)	Untreated LDL-C>13mmol/l(500mg/dl) or treated LDL-C≥8mmol/l(300mg/dl)
(c)	Cutaneous or tendon xanthoma before 10 years of age
(d)	Untreated raised LDL-C levels as per diagnostic criteria in both parents
For diagnosis: (a) / (b) Plus (c) OR (d) Alone	

International Journal Dental and Medical Sciences Research
Volume 3, Issue 1, Jan-Feb 2021 pp 1120-1124 www.ijdmsrjournal.com ISSN: 2582-6018

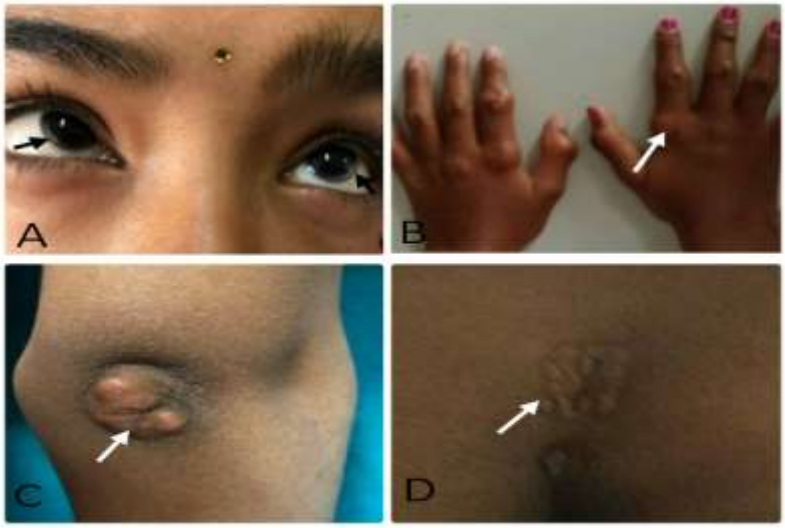

Fig.1

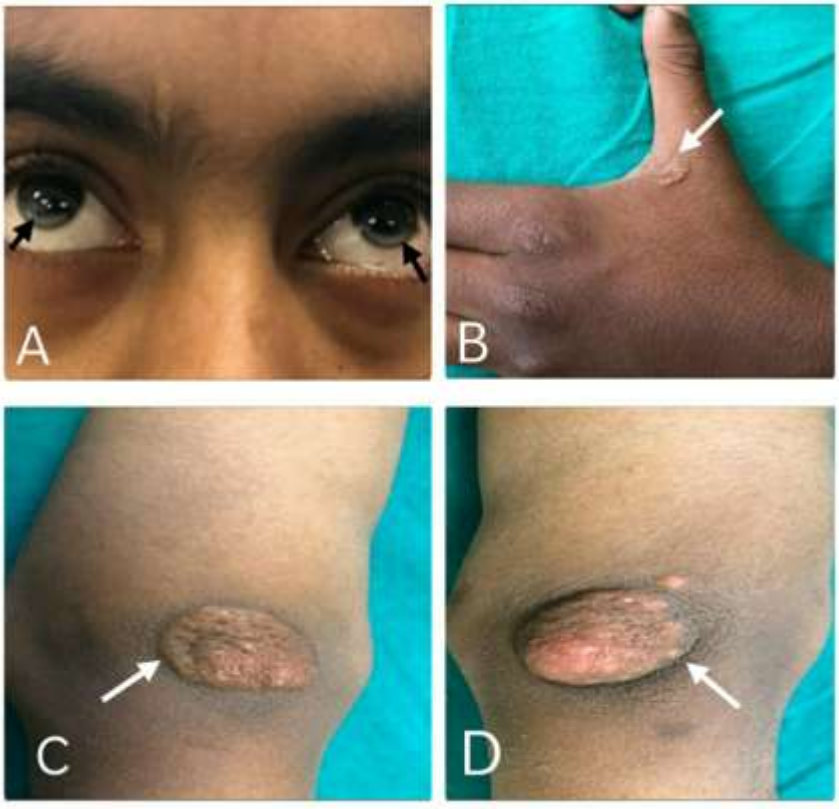

Fig.2