Homozygous familial hypercholesterolemia: Case report and review of literature

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Abstract: Familial hypercholesterolemia (FH) is a genetic disease presented by high levels of serum low density lipoprotein (LDL), xanthomas and early coronary artery disease (CAD). The diagnosis of Homozygous Familial Hypercholesterolemia (HoFH) is based on a family history of elevated cholesterol, persistent high LDL levels despite maximum medical treatment and the development of xanthomas and early atherosclerotic cardiac lesions such as aortic stenosis. Management of HoFH patients requires lifestyle modifications and medical therapy.

Keywords: Familial Hypercholesterolemia (FH), Homozygous Familial Hypercholesterolemia (HoFH), Xanthomas, Genetic Disease

1. Introduction

Familial hypercholesterolemia (FH) is a genetic disease presented by high levels of serum low density lipoprotein (LDL), xanthomas and early coronary artery disease (CAD). The main cause of FH is LDL receptor abnormalities that decrease the uptake of LDL into cells, particularly into the liver cells, from the blood, resulting in the increase of serum LDL-cholesterol levels.[1] The incidence of homozygous FH (HoFH) is very low (1 in million people). However, heterozygous FH occurs in 1 of 500 people, and is frequently detected by routine medical health check-up.[2-4] The incidence of acute myocardial infarction (MI) in FH patients' increases with the increasing age. [5,6] Management of HoFH patients require lifestyle modifications and medical therapy. If these do not work (as in most cases it does not), LDL apheresis and orthotopic liver transplant (OLT) are the only alternatives presently available, in the treatment of HoFH.

2. Case Report

A 5 year old female child presented with the chief complaints of multiple yellowish lesions over various parts of body for about four years. Child was apparently well till the age of 6 months, when her mother noticed yellowish brown lesions on both the legs. Lesions gradually increased in number and size. Fresh lesions also started appearing on buttocks, knees, foot, elbows, hands and face.

There was no family history of consanguinity, acute myocardial infarction, stroke, dyslipidaemia or xanthomas. Physical examination of the child showed: intertriginous xanthomas of the feet and hands (Figure 1a, 1b), tuberous xanthomas of the knees and elbows (Figure 2a, 2b), tendinous xanthomas in the Achilles tendon (Figure 3) and xanthomas in the gluteal region (Figure 4). Linear plaques were also present in the popliteal fossa and on the wrist. Solitary yellow nodule was present on the left side of the face near the medial canthus (Figure 5). A xanthoma was also present in the alveolar area of the upper jaw (Figure 6).

Fig 1a. *Xanthomas of feet.*

Fig 1b. *Xanthomas of hand.*

Fig 2a. *Xanthomas present at elbow joint.*

Fig 2b. *Xanthomas at knee joint.*

Fig 3. *Tendinous xanthoma.*

Fig 4. *Xanthomas at gluteal region.*

Fig 5. *Solitary nodule at left medial canthus.*

Fig 6. *Xanthoma in oral cavity.*

On investigations, plasma lipid levels of the child were: total cholesterol (TC), 796mg/dl; low density lipoproteins (LDL), 401mg/dl; triglycerides (TG), 121mg/dl and high density lipoprotein (HDL), 127mg/dl. On cardiac echo, coarctation of aorta was seen. Liver enzymes, renal functions, blood glucose, uric acid, free thyroxine and thyroid-stimulating hormones were normal. Plasma lipid levels of child's mother were also raised. Her levels were: TC, 268mg/dl; LDL, 196mg/dl; TG, 105mg/dl; HDL, 51mg/dl. Child's father expired in a road traffic accident two years ago. He had a history of cardiac problem (nature not known). Two elder siblings, one brother and a sister, had normal plasma lipid levels.

The diagnosis of HoFH was based on the clinical characteristics, very high LDL level of the patient (401 mg/dl) and her mother (her father had expired and hence could not be investigated), early age of onset and exclusion of secondary causes of dyslipidaemia.[7,8]

3. Discussion

Simon Broome formed criteria for definite and possible diagnosis of FH.

A definite diagnosis of FH is established if the case has:
♦ Cholesterol concentrations as defined in table 1.
♦ Tendon xanthomas, or evidence of these signs in first- or second-degree relative orDNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Our child had tendon xanthomas and also her LDL levels were 401mg/dl (>72mg/dl), conforming to the definite diagnosing of FH criteria's. FH can be homozygous (HoFH) or heterozygous.

The diagnosis of HoFH is based on a family history of elevated cholesterol, persistent high LDL levels despite

maximum medical treatment and the development of xanthomas and early atherosclerotic cardiac lesions such as aortic stenosis. A clinical diagnosis of HoFH is possible where LDL cholesterol > 13 mmol/L (234mg/dl) in adults and > 11mmol/L (198mg/dl) in children.[8] Where potential cases of FH are identified, an extensive family history must be obtained (ideally a three-generation pedigree) with particular attention given to relatives with significant vascular incidents, the age of onset of events, cardiovascular risk factors and any formal FH diagnoses.[8,9]

In our case, the diagnosis of HoFH was based on the early age of onset of clinical characteristics (since the age of 6 months), very high levels of LDL of the patient (401 mg/dl) and her surviving parent, and exclusion of secondary causes of dyslipidaemia.[7,8]

The patient also has coarctation of aorta as reported on echocardiography. No such association has been reported. Whether it is an association or coincidental is difficult to comment.

4. Review of Literature

Familial hypercholesterolemia (Type IIa of the Fredrickson classification) is inherited as an autosomal - dominant disorder of lipid metabolism. This genetic disorder is characterized by high cholesterol levels, specifically very high levels LDL and early onset of cardiovascular disease (as early as 1st decade of life).[10,11]There is mutation in the LDL receptor gene present over chromosome 19 that encodes the LDL receptor protein, which normally removes LDL from circulation.[12,13]Also there can be mutation in apolipoprotien B (ApoB), which is the part of LDL that binds with the receptor.[14,15]

There are five major classes of FH due to LDL receptor mutations: [12]

Class I: LDL receptor is not synthesized at all.

Class II: LDL receptor is not properly transported from the endoplasmic reticulum to the Golgi apparatus for expression on the cell surface.

Class III: LDL receptors do not properly bind LDL on the cell surface because of a defect in either apolipoprotein B100 or in LDL-R.

Class IV: LDL receptor bound to LDL does not properly cluster in clathrin-coated pits for receptor-mediated endocytosis.

Class V: LDL receptor is not recycled back to the cell surface.

There are two types of FH: the heterozygous form in which the patient has one normal allele and one mutated allele. This is the most common form with an incidence of 1:500. The other form is homozygous form in which the patient has two mutated alleles, considered an autosomal codominant disorder. This is rare with an incidence of approximately one in a million [2-4,16]Patients with heterozygous FH are usually diagnosed as adults and usually respond well to medical therapy. On the other hand, patients with HoFH are often diagnosed early in childhood,

do not respond well to medical therapy, and can progress rapidly to premature coronary artery disease.[17]

Dietary fat including cholesterol and triglycerides are absorbed in the intestine and released in the blood stream as chylomicrons. These are least dense particles having very high proportion of triacylglycerides. Lipoprotein lipase (LPL) acts on these particles to release some free fatty acids that deposit in adipose tissues. The remnants of chylomicrons are picked up by the liver which has a receptor specific to chylomicron remnants. After further clean up, liver releases these particles called the very low density lipoproteins (VLDL) in the blood. Once again LPL works on these VLDL particles releasing more free fatty acids and changing the content of the particles to intermediate density lipoprotein (IDL) and LDL. There are LDL receptors on the cell membranes of the extrahepatic cells which pick up the LDL particles. This is how cholesterol reaches the interior of normal cells. Within cells, LDL particles are repackaged. Excess cholesterol is esterified and stored. Excess cholesterol suppresses the biosynthesis of LDL-receptors so that intake of cholesterol decreases. It also suppresses cholesterol biosynthesis.[18]Repackaged LDL particles called HDL particles are then released into the blood stream. These particles are sensed by the liver through the HDL-receptors.

Myant[19] in 1973 first theorized that metabolism of LDLs and other cholesterol are closely related. LDL receptors present in the liver clear LDL micelles from plasma. LDL cholesterol normally circulates in the body for 2.5 days, and subsequently binds to the LDL receptor on the liver cells, undergoes endocytosis, and is digested. LDL is removed and synthesis of cholesterol by the liver is suppressed in the HMG-CoA reductase pathway. In FH, LDL circulates for an average duration of 4.5 days (due to LDL receptor mutations) resulting in significantly increased level of LDL cholesterol in the blood with normal levels of other lipoproteins.[20]

Increase LDL levels in blood result in atherosclerotic changes in arteries.[21,22]Furthermore, patients may develop accumulation of cholesterol in other parts of the body leading to the development of cutaneous xanthomas of various types like xanthelasma, xanthomatendineum, and xanthoma tuberosum.[10]

Management of familial hyper-cholesterolemia patients, especially homozygotes has been a challenging job. Beyond genetic counselling for patients and the families of the patients diagnosed with FH, treatment options involve decreasing serum cholesterol levels and increasing cholesterol removal. Therapies available include diet and lifestyle modifications focusing on a reduced-cholesterol diet, pharmacologic treatment affecting cholesterol absorption and metabolism, and LDL aphaeresis to remove LDL from the serum to decrease the levels.

5. Diet and Lifestyle

People with FH should be advised to consume a diet in

which:
- Total fat intake is 30% or less of total energy intake
- Saturated fats are 10% or less of total energy intake
- Intake of dietary cholesterol is less than 300 mg/day
- Saturated fats are replaced by increasing the intake of monounsaturated and polyunsaturated fats.

For lifestyle modification, strictly limit the food containing high cholesterol such as pork, beef, various animal internal organs and egg yolk etc. Eating more coarse food grains, fresh vegetables and fruits, increasing food fibres intake helps to expel cholesterol. But FH usually responds poorly to the low lipid diet. Total substitution of animal protein with textured soy proteins in the diet has been reported to reduce plasma total and LDL cholesterol concentrations, with variable effects on HDL concentrations in hypercholesterolemia patients. . Antonio gaddi et al [23]showed that Soy protein decreased TC (-20.8%) and LDL (-25.8%) levels in patients suffering from FH. But Cochrane reviews stated that, no conclusions can be made about the effectiveness of a cholesterol-lowering diet, or any of the other dietary interventions suggested for FH, due to the lack of adequate data.[24]

6. Pharmacological Treatment

Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of 10 years. But the AAP recommends that patients < 8 years of age should be treated pharmacologically when they present with persistent LDL concentrations > 500 mg/dL, which are generally present in patients with the HoFH.[25]

HoFH is mostly resistant to medical therapy. In HoFH both LDL receptor alleles are affected so that there is little to no LDL receptor activity to be up-regulated.

Statins or 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors have been shown to be effective at reducing coronary morbidity and mortality in high-risk adults. Statins competitively inhibit HMG-CoA reductase, which is the rate-limiting enzyme for endogenous synthesis of cholesterol.[26]Thus, by inhibiting this enzyme, the statins reduce plasma concentrations of TC and LDL. To a lesser extent statins reduce apolipoprotein B (ApoB) and TG and increase HDL levels. Due to the reduction in LDL concentrations, statins also cause upregulation of LDL receptors, resulting in an increased LDL clearance from the circulation.[27]Common mild adverse effects include headache, myalgias, and gastrointestinal symptoms (abdominal pain, dyspepsia, diarrhoea, constipation). Most adverse side effect of statins is myopathy which is seen in 0.1% to 1.0% of patients using statins.[28]Reservation regarding use of statins in children is that lipids play a key role in brain development, especially during the adolescent and young adult years when integration of signal processing and neurodevelopment occurs.[29]So the concerns exist regarding use of statins for long term in view of its unknown effects/alterations on the child's central nervous system,

energy function, growth and sexual hormones development, if used at such a young age. Initially, with the use of less potent statins, decrease in LDL levels was discouraging in HoFH. However, with the advent of the more potent statins, a clinically meaningful effect began to be observed in HoFH. In a study of eight HoFH patients treated with simvastatin 80 mg and 160 mg, the 80-mg dose produced a 25% reduction in LDL and the 160-mg dose produced 31% reduction. Seven of the eight patients were receptor defective, but in one receptor-negative patient, there was a 30% reduction in LDL.[30]

Other drugs which are used alone or in combination with statins are bile acid sequestrant and fibrates.[31]Since bile acids are biosynthesized from cholesterol, disruption of bile acid reabsorption will decrease cholesterol levels, in particular, LDL. Therefore, they are used for the treatment of hypercholesterolemia and dyslipidemia.[32] Cholestyramine, colestipol and colesevelam have all been used. Bile acid sequestrants mainly causes gastrointestinal symptoms and vitamin deficiency by binding to fat soluble vitamins like A, D, E and K.

The fibrates are a class of amphipathic carboxylic acids used along with statins in FH. Fibrates act by induction of lipoprotein lipolysis, increased removal of LDL particles and increase in HDL production and stimulation of reverse cholesterol transport.[33]Usually clofibrate, benzafibrate or gemfibrozil are used. Most fibrates can cause mild stomach upset and myopathy. Since fibrates increase the cholesterol content of bile, they increase the risk for gallstones.[34]

Ezetimibe is a drug that lowers cholesterol. It acts by decreasing cholesterol absorption in the intestine. It may be used alone, when other cholesterol-lowering medications are not tolerated, or together with statins. Ezetimibe localises at the brush border of the small intestine, where it inhibits the absorption of cholesterol from the intestine. In addition to this direct effect, decreased cholesterol absorption leads to an up regulation of LDL-receptors on the surface of cells leading to an increased LDL-cholesterol uptake into cells, thus decreasing the levels of LDL in the blood plasma which contribute to atherosclerosis and cardiovascular events.[35,36]

The ARBITER 6-HALTS study, reported at the 2009 annual meeting of the American Heart Association and in the New England Journal of Medicine, concluded that 2000 mg/day slow-release niacin, when added to statins, was more effective than ezetimibe in reducing carotid intima-media thickness, a marker of atherosclerosis.[37,38]

Probucol, a potent anti-oxidant and cholesteryl ester transfer protein (CETP) activator is associated with a lowered risk of cardiovascular events when used in FH. Probucol lowers the level of cholesterol in the bloodstream by increasing the rate of LDL catabolism.[39,40]Additionally, probucol may inhibit cholesterol synthesis and delay cholesterol absorption. Probucol is a powerful antioxidant which inhibits the oxidation of cholesterol in LDLs; this slows the formation of foam cells, which contribute to atherosclerotic plaques.[41]It is believed to act at

ABCA1.[42]Yamamoto A and colleagues[43] showed marked reduction in serum cholesterol of HoFH. Also probucol resulted in decrease of eruptive and tendon xanthomas. Baker and colleagues have used probucol in as young as 6 year old child with no side effects. Baker also stated that the effects of probucol in this therapeutically resistant disorder were better than expected.[44] Considered in relation to efficacy, safety, tolerance and convenience, probucol appears to be the most satisfactory treatment for HoFH currently available.

Mipomersen is a second-generation antisense oligonucleotide (ASO) targeted to human apolipoprotein (apo) B-100 which is a large protein synthesized by the liver that plays a fundamental role in human lipoprotein metabolism. Mipomersen inhibits apolipoprotein B production independent of LDL receptor function and thus works in HoFH.[45]Mipomersen predominantly distributes to the liver and decreases the production of apoB-100, the primary structural protein of the atherogenic lipoproteins including LDL, thereby reducing plasma LDL-cholesterol and apoB-100 concentrations. Mipomersen is given 200 mg/week subcutaneously. Parhofer reported that Phase III studies indicate that the LDL cholesterol concentration can be reduced by 25%-47%, lipoprotein (a) levels by 20%-40%, and triglyceride levels by approximately 10%.[45] Bell and colleagues[46] also seconded that mipomersen produced dose-dependent and prolonged reductions in LDL-cholesterol and other apoB-containing lipoproteins. Although the short-term efficacy and safety of mipomersen has been established, concern exists regarding the long-term potential for hepatic steatosis with this drug.

Lomitapide is one of a cluster of new agents in development that offer the hope of achieving near-normal LDL levels in FH patients. Lomitapide, is a small molecule inhibiting microsomal triglyceride transfer protein or MTP-I, for reducing LDL levels in HoFH. It is administered as once daily dose. CuchelM et al[47] showed that inhibition of the microsomal triglyceride transfer protein resulted in the reduction of LDL cholesterol levels in patients with HoFH, owing to reduced production of apolipoprotein B. However, the therapy was associated with elevated liver aminotransferase levels and hepatic fat accumulation.

LDL-apheresis has proven its clinical utility in patients who cannot be adequately treated by diet and drug therapy alone. Evans KD in his thesis also concluded that LDL apheresis is a safe and effective procedure in patients with severe FH, refractory to or intolerant of lipid lowering drug therapies, to prevent the onset or progression of cardiovascular events in this high risk population. Lefort B and colleagues also treated a 4 year old child of HoFH by LDL apheresis.[48]Direct adsorption of lipids (DALI) is the first LDL-apheresis method compatible with whole blood.[49]Apart from iron deficiency anaemia, no major side effects were observed. LDL-apheresis using the DALI system is associated with significant reductions in LDL-cholesterol without major side effects, even in a child weighing less than 20kg.[48]

Starzl[50] in 1983 first described orthotopic liver transplant (OLT) as a cure for FH. Since OLT addresses the underlying deficiency, the absence of properly functioning LDL-receptors in the liver, patients undergoing OLT have fast and long-lasting resolution of their hypercholesterolemia. Moreover, these patients may have resolution of atherosclerotic changes and cutaneous xanthomas as well. CastillaCabezas JA[51] did OLT for two siblings and found decrease in cholesterol levels to normal values. Four years later both were alive and both had normal liver and heart functions. The patient needed neither the cholesterol-lowering drugs, nor had the disease progressed. Usually transplantation should be done prior to the development of severe coronary artery disease or aortic stenosis, since these are the most common causes of morbidity and mortality in this population.

7. Conclusion

Familial hypercholesterolemia, in heterozygous form is a common disease but the homozygous form is seen rarely. In homozygous variant of FH, clinical features appear early in childhood along with early cardio-vascular involvement. HoFH cases should be diagnosed as soon as possible, so as to prevent early deaths due to cardiac involvement. There can be LDL receptor defect, receptor reduction or complete absence of LDL receptors in HoFH. That is why, it becomes tough to medically treat this condition as most of the drugs work on up regulation of LDL receptors. Newer drugs like probucol, mipomersen and lomitapide are showing promising results in treatment of HoFH. Also if medical therapy fails then, LDL apheresis or ocassionaly orthotopic liver transplant can be undertaken for the treatment of this disease.

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