Case Report

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Familial Hypercholesterolemia

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Abstract

We present a 15 year old boy presenting to the Department of Cardiology with complain of tuberous eruptions over knees and elbows not responding to the antilipidemic drugs. He has lost his elder brother at 10 years of age secondary to sudden cardiac death. Father was quite apprehensive to save his single child surviving. Child was nonobese, nondiabetic, nonhypertensive and belonged to low socioeconomic status. Lipid panel showed total cholesterol being 467mg/dl with LDL as 298 mg/dl with normal HDL and TG level. Patient was on highest dose of statin with life style modification but lipid panel were not in the way to regress, we thought to put the patient on PCSK 9 inhibitor which was ultimately available with much difficulty, to get some improvement. FH was a foe before the era of new antilipidemic drugs but it is a friend now with new therapeutic strategies.

Keywords: Familial Hypercholesterolemia; PCSK 9 inhibitor; LDL; HDL.

Introduction

Familial hypercholesterolemia (abbreviated as FH) is a genetic disorder characterized by very high levels of low-density lipoprotein and accelerated atherosclerosis resulting in premature CAD and CVA. It harbors mutations in LDLR gene that encode LDL receptor protein, which removes LDL from the circulation or apolipoprotein B (ApoB) which is part of LDL that binds with the receptor. People who have one abnormal copy (are heterozygous) of the LDLR gene have premature cardiovascular disease in 3rd decade. Having two abnormal copies (homozygous) cause severe cardiovascular disease in childhood. Heterozygous FH is a common genetic disorder, inherited in an autosomal dominant pattern, occurring in 1:500 people all over world; homozygous FH is rarest occurring in 1 in a million births [1]. Heterozygous FH responds to antilipidemic drugs but homozygous FH often does not respond to medical therapy and require LDL apheresis (removal of LDL in a method similar to dialysis) and occasionally liver transplantation. They manifest as xanthelasma palpebrarum, arcus senilis corneae, tendon xanthoma and tuberous xanthomas [2]. FH is associated with raised level of total cholesterol, markedly raised level of low-density lipoprotein (LDL), normal level of high-density lipoprotein (HDL), and normal level of triglycerides. Total cholesterol levels of 350-550 mg/dL are typical of heterozygous FH while total cholesterol levels of 650-1000 mg/dL are typical of homozygous FH. The LDL is typically above the 75th percentile. Mutations are detected in between 50 and 80% of cases. FH needs to be distinguished from familial combined hyperlipidemia in which triglyceride is increased and polygenic hypercholesterolemia.

Case

We represent a 15 year old boy presenting to the OPD of Department of Cardiology of All India Institute of Medical Sciences (AIIMS), Bhubaneswar with Xanthelasma and tuberous eruptions over knees and elbows not responding to the antilipidemic

drugs. He has lost his elder brother at 10 years of age due to sudden cardiac death. The elder child was on aggressive statin therapy and his lipid panel was unresponsive to statin therapy, one day he landed up in accelerating angina and before any coronary intervention was taken out, he succumbed to death. Father was quite apprehensive to save his single child surviving. Child was non obese, nondiabetic, nonhypertensive and belonged to low socioeconomic status. His liver enzymes and thyroid panel were absolutely normal. Lipid panel showed total cholesterol 467mg/dl with LDL as 298 mg/dl with normal HDL and TG level.ECG was within normal limit and LVEF (Ejection Fraction) was normal. Screening of lipid panel in parents revealed mother to be normolipidemic and father harbored dyslipidemia in form of LDL being 229mg/dl and TC being 356mg/dl and was on statin highest dose since his first child's death. Father was nonsmoker, nondiabetic, nonhypertensive and slim person. Previously the child was tried by penopoly of physicians with bile acid sequestrants, fibrates, CETP inhibitors including statins with no substantial benefit to lipid parameters. Patient was on highest dose of statin with life style modification but lipid panel were not in the way to regress, we thought to put the patient on PCSK 9 inhibitor with informed consent and ethics to generate new hope in this child which was ultimately available with much difficulty and it resulted in improvement in lipid panel substantially at three months.

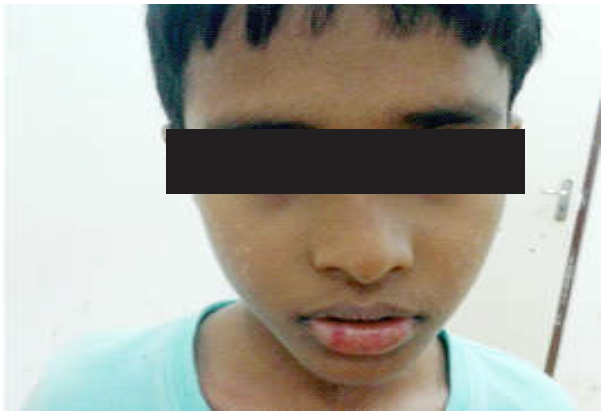

Fig. 1: Child having Xanthelsma

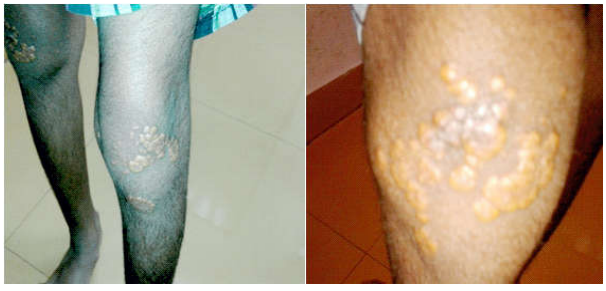

Fig. 2: Tuberous Xanthomas on both knees

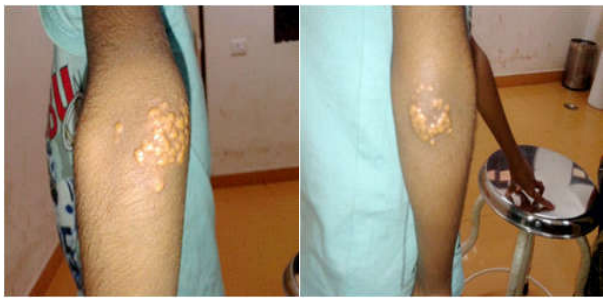

Fig. 3: Tuberous Xanthoma on both elbows

Discussion

The global prevalence of FH is approximately 10 million people [3]. Heterozygous FH occurs in about 1:500 people, but not all develop symptoms. Homozygous FH occurs in about 1:1,000,000. Ours is a rarest case of heterozygous FH to be infrequently observed in daily OPD practice. LDLR mutations are more common in certain populations because of a genetic phenomenon known as the founder effect. The Afrikaner, French Canadians, Lebanese Christians, and Finns have high rates of specific mutations that make FH particularly common in these groups where as APOB mutations are more common in Central Europe.

The Norwegian physician Dr C. Müller first described the physical signs, high cholesterol levels and autosomal dominant inheritance of this disease in 1938 [4]. In the early 1970s and 1980s, the genetic cause for FH was described by Dr Joseph L. Goldstein and Dr Michael S. Brown of Dallas, Texas. They described impaired binding of LDL to its receptor because of LDL receptor mutation resulting in significant surge in LDL level in this disease for which they were awarded Nobel Prize in Medicine in1985 [5]. The LDL receptor gene is located on the short arm of chromosome 19 . The plasma LDL levels are inversely related to the activity of LDL receptor (LDLR). Homozygotes have LDLR activity of less than 2%, while heterozygotes have defective LDL processing with receptor activity being 2–25%.

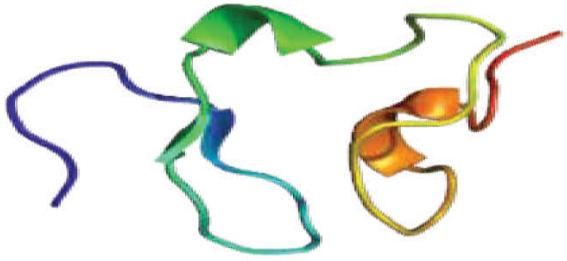

Fig. 4: Schematic representation of the LDL receptor

Here are five major classes of FH due to LDLR mutations [6]:

- Class I: LDLR is not synthesized at all.
- Class II: LDLR is not properly transported from the endoplasmic reticulum to the Golgi apparatus for expression on the cell surface.
- Class III: LDLR does not properly bind LDL on the cell surface because of a defect in either apolipoprotein B1 or in LDL-R.
- Class IV: LDLR bound to LDL does not properly cluster in clathrin-coated pits for receptor-mediated endocytosis.
- Class V: LDLR is not recycled back to the cell surface.

It has been suggested that PCSK9 causes FH mainly by reducing the number of LDL receptors on liver cells [7]. LDL cholesterol normally circulates in the body for 2.5 days and subsequently the apo B portion of LDL cholesterol binds to the LDL receptor on the liver cells, triggering its uptake and digestion. In FH, LDL receptor function is reduced or absent and LDL circulates for an average duration of 4.5 days, resulting in significantly increased level of LDL cholesterol in the blood with normal levels of other lipoproteins. Screening among family members, universal screening at the age of 16 have also been suggested. Guidelines recommend that the decision to treat a person with FH with statins should not be based on the usual risk prediction tools (such as those derived from the Framingham Heart Study), as they are likely to underestimate the risk of cardiovascular disease. There are no interventional studies that directly show mortality benefit of cholesterol lowering in FH. Surgical techniques include partial ileal bypass surgery, in which part of the small bowel is bypassed to decrease the absorption of nutrients and hence cholesterol, and portacaval shunt surgery, in which the portal vein is connected to the vena cava to allow blood with nutrients from the intestine to bypass the liver [8].

Given that FH is present from birth and atherosclerotic changes may begin early in life, it is necessary to treat adolescents or even teenagers with agents that were originally developed for adults. Due to safety concerns, many physicians prefer to use bile acid sequestrants and fenofibrate as these are licensed in children. Nevertheless, statins seem safe and effective, and in older children may be used as in adults. An expert panel in 2006 advised on early combination therapy with LDL apheresis, statins and cholesterol absorption inhibitors in children with homozygous FH at the highest risk [9]. PCSK 9 inhibitors now play a statutory role in statin resistant FH cases. We administered this child PCSK 9 inhibitor although this drug is a rarely available entity for which we faced a lot of difficulty. Dramatic reduction in plasma LDL level was observed at follow up at three months. All PCSK9 inhibitors are not yet approved for general use, and only one trial has been conducted so far [10] with Evolocumab which we used .Long-term efficacy and safety of these agents are yet to be investigated. However, clearly, these are very promising agents in the treatment of FH either as a monotherapy or as an adjuvant therapy.

Lomitapide, an inhibitor of the microsomal triglyceride transfer protein, was approved by the US FDA in December 2012 as an orphan drug for the treatment of homozygous familial hypercholesterolemia. In January 2013, The US FDA also approved mipomersen, which inhibits the action of the gene apolipoprotein B, for the treatment of homozygous familial hypercholesterolemia. Gene therapy is a promising future alternative.

Conclusion

Familial hypercholesterolemia is a devastating entity which creates LDL storm in blood in early life culminating in a premature death. The crux of this rare entity is that the surge in LDL does not respond usually to statins and diet therapy. Aggressive screening of this entity in early life with polypharmacy with newly approved drugs besides LDL apheresis may provide these children a new life. Gene therapy must come out in strong hold to rescue these children out of this lipid crisis. Ours case is a rare entity where we tried to provide a new hope to the parents with promising PCSK 9 inhibitors to come out of this cholesterol crisis. Further researches are needed to pave a new path in its treatment horizon.

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