

Role of LDL apheresis in a case of homozygous familial hypercholesterolemia

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Summary Familial hypercholesterolemia (FH) is a form of primary hyperlipoproteinemia characterized by the presence of high concentrations of serum low density lipoprotein (LDL) cholesterol, increased tendency to form xanthomas and early onset of coronary artery disease. This disease is an autosomal dominant disorder caused by defects in the gene that encode for the LDL receptor. Homozygous familial hypercholesterolemia is a rare occurrence and here we report a case of an 18-year-old girl with familial hypercholesterolemia treated with anti-lipidemic drugs and controlled only with LDL apheresis. The patient expired after 3 months highlighting the difficulties in management due to economic constraints in a resource limited setting in spite of availability of effective therapy.

Keywords: Autosomal dominant, xanthoma, coronary artery disease

1. Introduction

Familial hypercholesterolemia (FH), otherwise also referred to as autosomal dominant hypercholesterolemia type 1 is a genetic disorder of the lipoprotein metabolism. It is characterized by high levels of serum low density lipoprotein (LDL), eruptive xanthomas all over the body and premature atherosclerotic disease affecting the heart, aorta, carotids and peripheral arteries. Homozygotes for the disease are at 100 times greater mortality risk from fatal myocardial infarction (MI) due to premature atherosclerotic damage to the coronary arteries than those without the disease (1,2). Timely recognition of the disease and aggressive lipid lowering is lifesaving in these patients. We are presenting a case of 18-year-old female exhibiting characteristic features of familial hypercholesterolemia.

2. Case Report

An 18-year-old girl, with a body mass index (BMI)

of 17.7 kg/m² presented with eruptive xanthomas, gradually increasing in size over different parts of the body involving extensor surfaces of bilateral large and small joints of upper and lower limbs, thighs and gluteal regions since 8 years of age. The patient also had history of exertional shortness of breath and angina for which she was evaluated and found to have dyslipidemias along with severe valvular and supra-valvular aortic stenosis and antero-medial leaflet prolapse of mitral valve causing severe mitral regurgitation. The patient was started on anti-lipidemic drugs and diuretics. However, the patient did not improve to treatment with these drugs. She underwent double valve replacement 1 year ago following which she remained asymptomatic. Since then, the patient was on atorvastatin (60 mg), warfarin, aspirin, digoxin and furosemide.

The patient presented to our Out Patient Department (OPD) with fatigue and generalized malaise, increasing size and number of the skin lesions, with multiple reports showing very high levels of LDL (max. 959 mg/dL). Her triglycerides were also elevated while her high density lipoprotein (HDL) and very low density lipoprotein (VLDL) were within normal limit. On examination, she had xanthelasma palpebrarum over both the eyelids, multiple xanthomas over bilateral knuckles, fingers, elbows, knees, thighs and feet. Examination of eyes revealed arcus juvenilis and lipemia retinalis in both the

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Table 1. Lipid profile values at different time points

In mg/dL	October, 2010	August, 2013	July, 2016	First presentation Dec. 2016	Post 1st LDL apheresis	Before 2nd LDL apheresis	Post 2nd LDL apheresis
Total Cholesterol	624	676	689	746	156	479	116
Triglycerides	323	154	270	204	62	179	177
Low Density Lipoprotein	538.4	599	599	959	122	360	77
High Density Lipoprotein	21	47	36	35	23	71	17
Very Low Density Lipoprotein	64.6	68	54	40.8	11	48	22

eyes. Cardiovascular examination was unremarkable.

One of her 2 siblings, 2 years elder to her had history of similar eruptive xanthomas and atherosclerotic coronary artery and valvular heart disease. He expired following a fatal myocardial infarction at the age of 15 years. However, other sibling had no history of such lesions, but lipid profile showed dyslipidaemias albeit of less severity. There was no history of xanthomas and xanthelasma in her parents. There was no history of coronary artery disease, diabetes, hypertension in their paternal or maternal families.

Serial lipid profile of the patient was monitored (Table 1). Investigations were done to look for the evidence of end-organ damage due to the atherosclerotic disease. Electrocardiograph (ECG) showed left ventricular hypertrophy, chest X-ray was unremarkable except for metallic prosthetic valves, 2D echocardiography showed post dual valve replacement (DVR) status with normal prosthetic aortic and mitral valves and normal ventricular function. Computed tomography (CT) coronary angiography showed significant ostial stenosis of > 50% in left main coronary artery. Doppler of bilateral subclavian and renal arteries showed a high resistance flow. Fundus examination revealed an abnormal right optic disc with peripapillary vessels and perivascular glistening deposit suggestive of atheromatous deposits, normal left disc. Her blood sugar, thyroid function tests were normal. The patient was started on a high dose statin (rosuvastatin 40 mg per day), ezetimibe 10 mg per day, cholestyramine 32 mg per day and nicotinic acid 2 g per day along with a low-fat diet. In view of refractory hypercholesterolemia despite maximal doses of anti-lipidemic drugs she was given a session of LDL apheresis by cascade method following which LDL dropped from 517 mg/dL to 122 mg/dL. A 2nd session of LDL apheresis was done a fortnight after the first session following which her LDL level dropped to 77 mg/dL. The patient was discharged with an advice of strict compliance to diet, anti-lipidemic drugs, LDL apheresis and further follow-up. But due to economic constraints, LDL apheresis was not done on regular basis and later she presented to emergency and expired due to acute myocardial infarction.

3. Discussion

The first case of familial hypercholesterolemia (FH) was

described in medical literature by Carl Muller in 1939, who had described the triad of hypercholesterolemia, xanthomatosis and angina pectoris which was inherited in an autosomal dominant mode (2). It was Berg and Goldstein in 1985 who had reported that the increased level of LDL in blood was due to defective LDL receptors in the cells causing a decrease in absorption of LDL into the cells-especially the hepatocytes which are responsible for clearing about 70% of LDL from the body. Furthermore, due to decrease in the absorption of LDL in the liver cells, there is no suppression in the synthesis of cholesterol and LDL by the liver thereby leading to a further increase in the total cholesterol and LDL in the body (3). Increased circulating cholesterol also leads to an increase in the uptake of cholesterol in the non-hepatic cells leading to the adverse effects of hypercholesterolemia. FH is amongst the first genetic disorders to be discovered which are caused due to a defect in the genes encoding for a receptor, it is also the first genetic disorder recognized to cause Myocardial Infarction (3,4).

The prevalence of heterozygous FH is about 1 in 500 people making it a very common disorder in the population. Homozygous FH, however is much rarer and is present in only 1 among a million people. The disorder exhibits a gene dose effect with those homozygous for the disease exhibiting eruptive tendonxanthomas, xanthalesmas in the first decade of their life, usually starting at the age of 4 years. Such patients have very high LDL levels, in the range of 650-1,000 mg/dL and usually die of complications of atherosclerotic heart disease (AHD) by the age of 20 years without adequate treatment. Heterozygotes for the disease usually develop xanthomas by their second or third decade of life and atherosclerotic disease of the heart and blood vessels by their third decade of life. LDL levels in heterozygotes are usually in the range of 250-550 mg/dL. Heterozygotes for the disease are at a more than 50% cumulative risk of fatal or non-fatal coronary heart disease by age of 50 years. This risk is significantly increased in homozygotes of FH and as mentioned previously they are 100 times more likely to experience a fatal MI than general population (1,2).

Homozygotes for FH are further classified into 2 groups – patients with less than two percent LDL receptor activity and patients with LDL receptor activity greater than 2 percent but less than 25 percent

of normal. Plasma LDL levels have an inverse relation to the remaining LDL receptor (LDL-R) activity (5). The former group performs very poorly and without treatment succumbs to atherosclerotic heart disease by the age of 20 years. The latter group has a better prognosis and develops atherosclerotic disease by the third decade of life. Early and aggressive treatment to lower the LDL and total cholesterol levels with antilipidemic drugs as well as LDL apheresis in patients of FH is thus lifesaving.

Over 1,600 mutations in the LDL receptor gene have been identified which cause FH. Five different genetic variants of FH have been identified by Tosi *et al.* in 2007 with each class having multiple alleles (6). Class 1 mutation – These are "null allele" mutations in which LDL-Rs are not produced due to large deletion mutations. Class 2 mutations – These are the most common mutations. They are caused due to the failure of the receptors to migrate to the cell surface. Class 3 mutations – These mutations lead to a defective APO-B component of LDL due to which LDL is unable to bind to its receptors. Class 4 mutations – These mutations result in the defective internalization of LDL-LDL receptor complexes. Class 5 mutations – These mutations interfere with the LDL receptors ability to recycle back to the cell surface.

Raised LDL levels with few phenotypic similarities to familial hypercholesterolemia are also present in conditions like familial combined hypercholesterolemia, familial defective apolipoprotein B-100, autosomal recessive hypercholesterolemia (ARH), polygenic hypercholesterolemia and sitosterolemia.

In our case the patient was clinically diagnosed with familial hypercholesterolemia, in view of the appearance at the age of 8 years of eruptive xanthomas over the extensor surfaces of bilateral large and small joints, thighs and gluteal regions. She also had the rare intertriginous xanthomas which have been described as pathognomonic for homozygous FH (7). At the same time she also had developed severe valvular heart disease secondary to premature atherosclerosis. After hospital admission patient was also diagnosed with an ostial narrowing of the left main coronary artery characteristic of atherosclerotic damage. There was also arcus juvenilis and lipemia retinalis in the eyes. The patient had responded to aggressive lipid lowering with the use of statins, bile acid resins, ezetimibe along with LDL apheresis, which resulted in significant decrease in the size of her xanthomas and also subjective improvement of her fatigue and generalized malaise. The patient had a first degree relative who had also developed similar eruptive xanthomas

and had succumbed to a fatal MI due to premature atherosclerotic coronary artery disease (CAD). The patient has a brother who is currently 22 years old and although he does not have eruptive xanthomas/xanthelasma, he was found to have dyslipidemia on routine evaluation. Our patient also satisfies the WHO criteria for familial hypercholesterolemia (score > 8).

4. Conclusion

The clinical features and biochemical profile of this patient are consistent with homozygous familial hypercholesterolemia with atherosclerotic end organ damage. It is a rare disorder of lipid metabolism that is under diagnosed and under treated. Early detection and aggressive lipid lowering therapy with statins, non-statin along with regular LDL apheresis is recommended. LDL apheresis has definitive role in homozygous FH and it should be regularly done to maintain target level to prevent atherosclerotic complications. However if LDL apheresis cannot bring LDL levels to the recommended target level then patient may have to be considered for liver transplantation. Limited availability and economic issues are major concerns in management of these patients in a resource limited setting.

References

1. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: A HuGE prevalence review. *Am J Epidemiol.* 2004; 160:407-420.
2. Muller C. Angina pectoris in hereditary xanthomatosis. *Arch Intern Med.* 1939; 64:675.
3. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science.* 1986; 232:34-47.
4. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. *Hum Mutat.* 1992; 1:445-466.
5. Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest.* 2003; 111:1795-1803.
6. Tosi I, Toledo-Leiva P, Neuwirth C, Naoumova RP, Soutar AK. Genetic defects causing familial hypercholesterolemia: Identification of deletions and duplications in the LDL-receptor gene and summary of all mutations found in patients attending the Hammersmith Hospital Lipid Clinic. *Atherosclerosis.* 2007; 194:102-111.
7. Sethuraman G, Thappa DM, Karthikeyan K. Intertriginous xanthomas – a marker of homozygous familial hypercholesterolemia. *Indian Pediatr.* 2000; 37:338.

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