

Accelerated Atherosclerosis in a Young Female with Familial Hypercholesterolemia

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Abstract

Familial hypercholesterolemia is an autosomal dominant genetic disease due to mutation in low-density lipoprotein-cholesterol receptor gene. It is characterized by elevated plasma low-density lipoprotein-cholesterol and the consequence of which leads to premature cardiovascular disease. The mainstay in the management of familial hypercholesterolemia patient is the treatment with high potency statin. However, current research shows influence of the type of low-density lipoprotein-cholesterol receptor mutations on severity of the cardiovascular disease, lipid profile, and response to statin treatment. We are here presenting a case of young Indian female patient who was diagnosed with familial hypercholesterolemia and treated with percutaneous trans-luminal coronary angioplasty in view of double vessel disease in the third decade of her life. She was prescribed with statin therapy for elevated low-density lipoprotein cholesterol. After 3 years, she presented once again with a triple vessel disease along with patent stented segments and abnormal lipid profile.

Keywords

Familial Hypercholesterolemia, Premature Coronary Artery Disease, Statin

1. Introduction

Heterozygous familial hypercholesterolemia (FH) is an autosomal dominant genetic disease. Due to the mutation in low-density lipoprotein-cholesterol receptor (LDLR), the disease is characterized by elevated level of plasma low-density lipoprotein-cholesterol (LDL-C) and thereby increases the incidence of premature cardiovascular disease (PCVD) in the affected individuals in the early decades of their lives [1]. The occurrence of

the PCVD can be prevented by providing adequate treatments but it has been found that only 5% of the individuals, affected by FH, are treated adequately [2] [3]. In addition, current research ascertains that the lipid profile as well as response of patient to statin treatment depends upon the type of LDLR gene mutation [4]-[6].

We are here presenting a case of young female who was clinically diagnosed with FH in the third decade of her life. Even though the patient was aggressively treated with life style modification and with pharmacological therapy, her lipid profile remained abnormal and she experienced cardiovascular disease repeatedly. This case-report highlights the need to determine the influence of LDLR gene mutation in response to statin therapy. So, the patient can be treated adequately to prevent PCVD based upon the knowledge of type of gene mutation.

2. Case Report

A 30 years old female attended the clinic for a regular check-up. She was of normal built, having BMI of 28.8 kg/m². She was normotensive and non-diabetic. She complained about the multiple yellowish plaques over knees, ankles and buttocks.

Upon examinations, we found tendon xanthoma over knees, ankles and buttocks along with xanthelasma on eyelids and corneal arcus. Her laboratory investigations also revealed abnormal lipid profile (Table 1).

Her family history was suggestive of abnormal lipid profile in the early decades of life (Table 2) as well as tendon xanthomas in her three siblings. She denied having coronary artery disease (CAD) or pre-mature death of family member due to CAD.

Other laboratory examinations, *i.e.* thyroid function tests (T3, T4 and TSH), liver function tests (AST, ALT, γ -GGT) and renal function tests (serum creatinine, urinalysis) were normal. We clinically diagnosed the patient with FH. The genetic analysis would conclude if she is having homogeneous FH or heterogeneous FH. A systemic examination (electrocardiogram [ECG], two-dimensional echocardiogram, treadmill test) of the cardiovascular system revealed normal findings. The patient was prescribed ATOCOR-E (atorvastatin 10 mg + ezetimibe 10 mg) along with life style modifications.

Table 1. Lipid profile of the patient at the time of diagnosis, follow-up and at the time of presentations of coronary artery disease.

Parameters	Normal laboratory values	At the time of initial diagnosis	At the time of 1st time presentation of CAD	During follow-up	At the time of 2nd time presentation of CAD
Total Cholesterol (mg/dL)	<200	462	463	390	444
Triglycerides (mg/dL)	<150	70	62	79	100
Low-density lipoprotein-cholesterol (mg/dL)	<100	287	293	255	384
High-density lipoprotein-cholesterol (mg/dL)	>60	NA	56	47	40
Apolipoprotein (mg/dL)	<30	NA	NA	NA	22.9

Table 2. Lipid profile of the siblings of the patient.

Parameters	Lipid profile of the siblings				
	40 years/female	30 years/Male	28 years/Male	25 years/Male	23 years/Male
Total Cholesterol (mg/dL)	207	190	269	351	313
Triglycerides (mg/dL)	97	87	109	118	119
Low-density lipoprotein-cholesterol (mg/dL)	146	133	204	286	241
Very low-density lipoprotein-cholesterol (mg/dL)	19	17	21	23	23
High-density lipoprotein-cholesterol (mg/dL)	42	40	44	42	49
Xanthoma	No	No	Present	Present	Present

After 2 months of the diagnosis, she presented to the clinic with the complaints of chest pain. ECG was suggestive of acute anterior wall ST elevation myocardial infarction (MI) which was thrombolysed with streptokinase. She underwent coronary angiography which revealed double vessel disease (DVD) (**Figure 1(A)**) for which she underwent percutaneous transluminal coronary angioplasty (PTCA) with 3×16 mm stent placement to mid segment of left anterior descending artery (LAD) and 3×10 mm stent in second obtuse marginal (OM) branch of left circumflex artery (LCX) (**Figure 1(B)**). She was discharged on ROSUVAS (rosuvastatin 20 mg), antiplatelets (aspirin/clopidogrel 150/150 mg for 1 year followed by aspirin/clopidogrel 150/75 mg), Starpress XL (metoprolol 50 mg twice daily) and Cardace (ramipril 5 mg). There was no complication observed during follow-up period but the lipid profile was still remained abnormal.

After 3 years of PTCA, the patient again came to the clinic with same complaints of rest angina since 2 days, not responding to sublingual nitrates. She also had shortness of breath (NYHA class II). She denied having any history of palpitations, syncope or easy fatigability. Her fasting lipid profile is shown in **Table 1**. Hematogram and other biochemical investigations were within normal range. ECG showed non-specific ST and T changes while cardiac biomarkers were not elevated. Echocardiogram showed good biventricular function with no gross abnormality. After initial medical therapy, she underwent coronary angiogram which showed triple vessel disease (TVD), diffuse narrowing of the proximal and mid segments of right coronary artery with 100% occlusion in distal segment, diffuse narrowing with 90% stenosis in the proximal segment of LCX showed and diffuse narrowing with 60% stenosis in the proximal segment of LAD (**Figure 1(C)** & **Figure 1(D)**). However the previously stented segments were patent with TIMI-III flow. In view of unfavorable anatomy, she was referred to surgeon for coronary artery bypass grafting.

3. Discussion

Here, in this case-report we have described a case of young female patient who had been diagnosed with FH based upon Dutch lipid clinic network criteria [3], *i.e.* elevated level of LDL-C (287 mg/dL), presence of tendon xanthoma, xanthelasma and corneal arcus, first degree relative with raised LDL-C along with xanthoma. We had

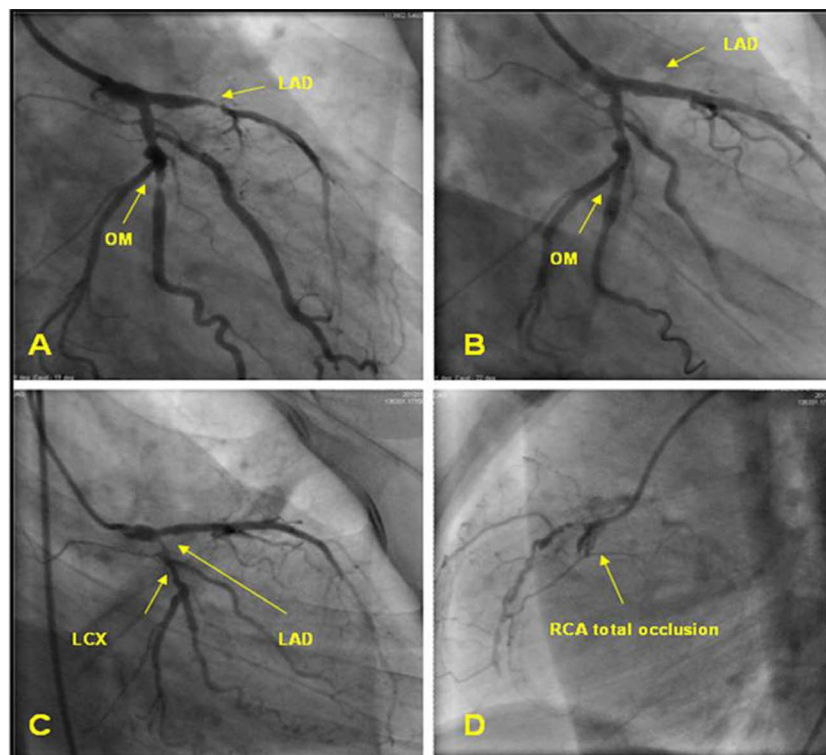


Figure 1. (A) First coronary angiography revealed double vessel disease; (B) Post-PCI of double vessel disease; (C) & (D) Coronary angiograph demonstrated triple vessel disease after three years of first PCI.

ruled out other possible clinical conditions (thyroid dysfunction, nephrotic syndrome, medications) that may lead to hypercholesterolemia. The patient was clinically (based on phenotype) diagnosed with FH. The cardiovascular system was found normal. As the patient was at high risk of development of coronary heart disease, we advised the patients to modify life-style along with pharmacological treatment—atorvastatin and ezetimibe. However, she developed DVD after 3 months of diagnosis for which PTCA was carried out. As the lipid profile was not achieved by the combination therapy of atorvastatin and ezetimibe, we prescribed rosuvastatin to the patient along with pharmacological treatment (metoprolol and ramipril) to prevent remodelling and arrhythmias in view of post-MI with left ventricular dysfunction. Even though the patient was prescribed high-dose statin therapy, she developed TVD after three years of PTCA. It is noteworthy that lipoprotein level was found normal in our patient.

The influence of the type of LDL-receptor mutations on lipid profile, severity of coronary artery disease and on response to treatment is not completely clear, and few studies have been performed with controversial findings. Our case-report strengthens the finding that the type of mutations of LDLR influences severity of coronary artery disease, lipid profile and response statin treatment.

Based on phenotypic effects, five classes of LDL-receptor mutations have been proposed. Class-I mutations are non-allele mutations. Due to large deletions and promoter mutations (Class-I mutations), there is no detectable LDL receptor protein. Class-II mutations (transport defective alleles) cause either complete (Class-II a) or partial (Class-II b) block of the transport of the LDL receptor from the endoplasmic reticulum to the Golgi apparatus. Defective LDL binding results in Class-III mutations and Class-IV mutations cause a deficiency in the internalization of LDL and Class-V mutations fail to recycle effectively.

Alonso *et al.* in their large cross-sectional studies found that the patients carrying null-mutations had significantly higher frequency of PCVD (1.7 folds higher) and recurrence of cardiovascular events [7]. Similar observations were also seen in other studies [8] [9]. The mutations of LDLR gene also affect severity of cardiovascular disease [7] [10] [11]. Junyent *et al.* had carried out a study to determine the effects of different mutations in LDLR gene and coronary heart disease by considering carotid intima-media thickness and they found that null-allele mutations of LDLR gene show more severe clinical phenotype independent of age, gender, lipid and non-lipid risk factors and cholesterol-year scores [5]. In addition to severity of coronary heart disease, it has been found out that the patients with receptor-negative (null-allele) mutations of LDLR gene show more severe lipid phenotype than those with receptor-defective mutations [11]-[13]. However, the studies show controversial results for the association between type of LDLR gene mutations and response to statin treatment. Sun *et al.* has observed no association between response to simvastatin treatment and LDL-receptor defects in 42 patients diagnosed with heterozygous FH [14]. Similar conclusion was observed in the study carried out by Sijbrands *et al.* [15]. On the other hand, Chaves *et al.* observed poor responses to statin treatment in patients with null-allele mutations when compared to the response of defective mutations [16]. Miltiadous *et al.* also indicated class V mutations exhibit better response as compared to class-II mutations in 49 patients [6].

In our case, due to cost consideration we could not carry out genetic analysis to confirm the type of mutation. However, this case highlights the need of research in this area so that the patient can be adequately treated and thereby PCVD can be prevented or delayed.

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