CASE REPORT

Familial hypercholesterolaemia presenting with coronary artery disease in a young patient

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SUMMARY

A man in his early 20s presented with an angina on exertion and postprandial angina. Upon examination, the patient had carotid artery bruit and multiple tendon xanthomas. His lipid profile showed a very high total and low-density lipoprotein cholesterol; treadmill test was strongly positive. Subsequent coronary angiogram revealed triple vessel disease. The patient underwent revascularisation and is on lipid lowering therapy.

BACKGROUND

Familial hypercholesterolaemia (FH) is a form of genetic or primary dyslipidaemia, which affects 0.2% of the population. It is the second most common form of the genetic dyslipidaemias after familial combined hypercholesterolemia (FCH)¹ and is characterised by an increase in low-density lipoprotein (LDL) cholesterol. The defect lies in the LDL receptors located in the liver and other organs owing to a possible mutation occurring in the LDL receptor gene located in the short arm of chromosome 19. However, the disease remains seriously underdiagnosed. Early detection and aggressive treatment are the keys. Screening of first-degree relatives play an important role and need to be emphasised.

CASE PRESENTATION

A 24-year gentleman presented with a history of chest pain on exertion, typical of angina since 3 months, initially NYHA class II, now progressed to class III. History of postmeal angina was present. However, he did not have shortness of breath, palpitations or syncope. The patient was not hypertensive or diabetic. He was a smoker, quit since 6 months. Family history of coronary artery disease (CAD) and dyslipidaemia was present. His father and elder brother were diagnosed with CAD and had a very high cholesterol levels predominantly LDL cholesterol.

Upon examination the patient was of an average build. Clinically stable with a pulse rate of 76/min, normal blood pressure and absence of pallor, pedal oedema, clubbing or cyanosis. Bilateral carotid artery bruit was present. He had multiple xanthomas over elbow, Achilles tendon, fingers and buttocks (figure 1) with arcus corneae. His cardiovascular and other system examination was normal.

INVESTIGATIONS

The lipid profile revealed a total cholesterol of 502 mg/dl; an LDL of 461 mg/dl, a high-density lipoprotein (HDL) of 27 mg/dl, a very low-density

lipoprotein (VLDL) of 14 mg/dl and triglycerides (TG) of 69 mg/dl. The haemogram and rest of biochemical investigations were normal. His ECG showed left ventricular hypertrophy and no significant ST/T changes. Echocardiography was normal with good left ventricular function. Treadmill test was strongly positive at 5.3 METs.

His coronary angiography revealed minimal left main coronary artery disease with ostial left anterior descending artery (LAD) showing 40% stenosis followed by 90% stenosis in proximal segment, circumflex artery (LCX) was dominant and showed discrete 95% stenosis in the distal part and non-dominant right coronary artery showed 95% ostial stenosis (figure 2).

DIFFERENTIAL DIAGNOSIS

FCH is the most common genetic differential diagnosis. FCH is also an autosomal dominant disorder. The prevalence may be as high as 1:100. The phenotype is characterised by an excess of ApoB-containing lipoproteins. This may manifest as excessive LDL, excessive VLDL or a combination of both. Tendon xanthomata does not occur. Definite diagnosis requires lipid information from multiple family members. Secondary causes of severe LDL hypercholesterolaemia include hypothyroidism, nephrotic syndrome, obstructive liver disease and drugs. Secondary causes should always be excluded.

TREATMENT

The patient underwent percutaneous transluminal coronary angioplasty with stent implantation to LAD and LCX. He was treated with dual antiplatelet agents, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitors (high-dose atorvastatin 80 mg/day), ezetimibe, β -blockers and ACE inhibitors.

OUTCOME AND FOLLOW-UP

Xanthomas softened upon treatment with atorvastatin. The patient is relieved of angina and is on follow-up. But his lipid profile remained in the same range during follow-up. The patient was advised LDL-apheresis, but it could not be performed owing to financial constraints.

DISCUSSION

Hyperlipidemia is caused by increased concentrations of plasma lipoproteins. Alterations resulting from genetic defects are classified as primary disorders of lipoprotein metabolism. Alternatively, other factors that alter lipoprotein metabolism, such as

To cite: Subramani KS, Kolhari VB, Manjunath CN, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-008718

Figure 1 Figure showing typical xanthoma.

diabetes mellitus or hypothyroidism, are classified as secondary disorders of lipid metabolism. The triad hypercholesterolaemia, xanthomatosis and angina pectoris have been recognised as a dominantly inherited syndrome since the work of Muller (1939).² Till date, more than 400 different mutations resulting in the FH phenotype have been described.³ Plasma levels of LDL-C are elevated at birth and remain so throughout life. Plasma TG levels are typically normal, and HDL-C levels are normal or reduced. FH is associated with a much higher risk for the development of CAD than are other forms of hypercholesterolaemia.⁴

FH is a monogenic, autosomal dominant disorder that occurs in the heterozygous form in approximately 1 in 500 individuals. Homozygotes are found approximately 1 in a million.⁵ The total cholesterol values are much higher in the homozygous variant (500–1000 mg/dl) as compared with those of heterozygous forms (325–450 mg/dl). Incidence of premature CHD is much earlier in the homozygous forms (second decade) and xanthomas occur in the first decade.

Figure 2 Coronary angiogram showing significant atherosclerotic lesions in both left (A) and right (B) coronary arteries.

Clinically, FH is characterised by deposits of cholesterol in the vascular wall, causing atheromas and extravascularly in the form of xanthomas. According to the Simon Broome Register Group, definite FH is defined as a TC concentration >7.5 mmol/l (290 mg/dl) or an LDL-C concentration >4.9 mmol/l (190 mg/dl) together with the presence of tendon xanthomas either in the patient or in a parent, child, grandparent, sibling, uncle or aunt.⁶

The index case had a TC of 502 mg/dl with an LDL-C of 461 mg/dl. There was a strong family history of coronary artery disease, with abnormal lipid profiles. This patient was suffering from angina for the past 3 months. His angiography revealed triple vessel disease. There were diffuse tendon xanthomas over his body. We report this case because of the rarity of the condition (incidence of 1/million).

The index case being the homozygous variant of FH would respond little to drug therapy. High-dose drug therapy using combinations of HMG CoA inhibitors, Nicotinic acid and fibrates must be used. However, if multidrug regimens do not exhibit sufficient therapeutic results,⁷ the LDL-apheresis is used for treating FH concomitantly. Mabuchi *et al*⁸ found that the combination of pharmacotherapy and LDL-apheresis facilitated the reduction of LDL-C levels by 60%. But it is expensive and has to be performed on a biweekly basis. Patients have been successfully treated with liver transplant⁹ but these are case reports. Partial ileal bypass has also been tried. Lomitapide has recently been approved by the FDA for treatment of FH. It inhibits the microsomal triglyceride transfer protein which is necessary for VLDL assembly and secretion in the liver. Gene therapy is still experimental.¹⁰ An anti-PCSK9 (proprotein convertase subtilisin/kexin type 9) antibody reduces LDL-C on top of a statin and is under trials.¹¹ Mipomersen sodium (ISIS-310 312), a synthetic second-generation antisense oligonucleotide that targets mRNA encoding apolipoprotein B-100. Mipomersen has displayed dose-dependent efficacy in lowering LDL-C, ApoB, triglycerides, total cholesterol in patients on stable lipid-lowering therapy for FH.¹²

Learning points

- ▶ Familial hypercholesterolemia should be suspected in young patients presenting with coronary artery disease, especially with a strong family history.
- ▶ Screening of first-degree relatives plays an important role in early detection and treatment.
- ▶ Aggressive treatment of hypercholesterolaemia and control of risk factors will help reduce the morbidity and mortality associated with this disease.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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