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Case Report

CASE REPORT

Homozygous familial hypercholesterolemia with an update on cholesterol management

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Abstract

Familial hypercholesterolemia (FH) is an autosomal dominant condition that increases the risk of premature cardiovascular disease. Despite advances in treatment, it remains under detected and under treated. As an inherited condition, it poses a risk to the patient and family members. Most cases are due to defective low-density lipoprotein receptor (LDLR) activity. Heterozygous mutations are common (1:250–1:300). Homozygous FH is very rare (2–3 in a million), with higher circulating cholesterol levels and a poorer cardiovascular prognosis. We present the management of a case of homozygous hypercholesterolemia due to homozygous LDLR mutation. The patient subsequently developed severe coronary artery and aortic valve disease despite aggressive lipid-lowering therapy. We review advanced lipid management options that include lipoprotein apheresis, Proprotein Convertase Subtilisin/Kexin type 9 inhibition, and the microsomal triglyceride transfer protein inhibitor lomitapide.

INTRODUCTION

In familial hypercholesterolemia (FH), increased low-density lipoprotein cholesterol (LDL-C) accelerates atherosclerotic cardiovascular disease (ACVD). Most commonly this is caused by mutations in the low-density lipoprotein receptor (LDLR) gene, but rarely (∼5% of cases) mutations in Apolipoprotein B-100 (APO-B), the ligand for LDLR, Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9), Apolipoprotein E or LDLR adaptor protein genes are responsible. We present a rare case of extreme hypercholesterolaemia due to homozygous mutation in LDLR, complicated by multi-vessel coronary artery disease (CAD) and aortic stenosis (AS).

CASE REPORT

A 56-year-old Indian man presented to endocrine services in 2012 with total cholesterol levels of 22 mmol/l [normal <4.0 mmol/l]. He was asymptomatic. Corneal arcus and tendon xanthoma (dorsum of both hands, pre-tibial and Achilles tendons) were present (Fig. 1). There was an ejection systolic murmur, normal peripheral pulses, and no organomegaly. Genotyping confirmed homozygous FH (HoFH) due to two LDLR gene mutations (the pathogenic p.Pro685Leu variant, identified in 25/2600 index FH cases, and once in homozygosity in large French database). The parents were first cousins. Interestingly, there was no family history of premature ACVD. His father

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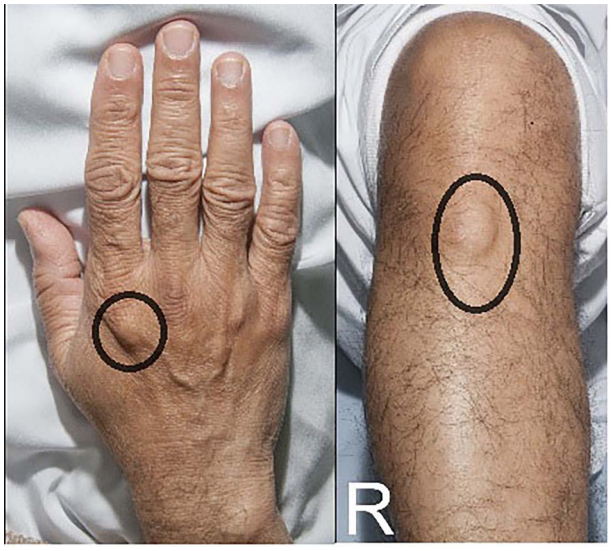

Figure 1: Pathognomonic signs of FH: tendon xanthoma deposits of cholesterol rich fat on the dorsum of both hands and knees.

died aged 82 and his mother aged 90. His three siblings have no known ACVD. Mandatory cascade testing showed high LDL levels in all six daughters with heterozygous FH (HeFH) status in all children. He has a history of hypertension managed on three agents. He worked as a teacher and does not drink alcohol or smoke. His lipid-lowering interventions are summarized in (Fig. 2). Although LDL apheresis produced an ~83% reduction in LDL-C immediately after apheresis, LDL-C levels returned to baseline within days, and interval mean LDL-C remained high. Multiple interruptions to LDL-apheresis occurred due to arteriovenous fistula failure, which ultimately occluded after 18 months.

Cardiac computed tomography (CT) to screen for ACVD, confirmed multi-vessel CAD with extensive calcification of the ascending aorta, aortic valve, and posterior mitral annulus (Fig. 3). Echocardiography confirmed severe AS (valve area: 0.5 cm^2). Due to the hostile aortic root precluding coronary artery bypass grafting, transcutaneous aortic valve implantation and percutaneous coronary intervention were recommended.

DISCUSSION

Anichkov first demonstrated the role of high cholesterol in atherosclerosis in 1913 [1]. Subsequently, the molecular basis of hypercholesterolemia has been determined [2]. HeFH is the most common inherited cardiovascular disorder (prevalence of 1:250–300), increasing premature ACVD risk ~20-fold [2]. HoFH is very rare and life threatening. Characterized by > 4-fold increase in LDL-C from birth, the first major cardiovascular event is frequently in adolescence but occasionally early childhood [3]. Early diagnosis and treatment improve clinical outcomes.

European Society of Cardiology (ESC) guidelines emphasize a goal-targeted approach to reduce LDL-C for very high cardiovascular disease (CVD) risk patients [4]. Hyperlipidemia Education and Atherosclerosis Research Trust in the UK recommends an LDL-C target of 1.8 mmol/L and 2.5 mmol/L for HoFH patients with, and without, ACVD respectively. Patients may fail to reach desired targets despite aggressive treatment, here the aim to achieve the maximum reduction with minimum side effects [3, 4]. Persistent hypercholesterolemia despite combination triple therapy (statin, ezetimibe and fenofibrate) triggers specialist lipid clinic referral.

Colesevelam, a bile acid sequestrant, which typically achieves ~16% LDL-C reduction, was tried but discontinued due to gastrointestinal side effects. LDL-C remained high, fulfilling criteria for LDL-apheresis.

LDL-apheresis, although not widely available, is highly effective at LDL removal (by 50–70%) from plasma, reducing cardiovascular events by 80–90% [2]. However, target interval LDL-C levels may not be achieved despite immediate post-treatment reduction. For example, our patient's interval LDL-C values were 11.8 mmol/l with LDL apheresis every 2 weeks.

PCSK9 inhibitors are monoclonal antibodies inhibiting degradation of LDLR, thus increasing cholesterol clearance by hepatocytes [2]. Two Food and Drug Administration-approved PCSK9 inhibitors, alirocumab and evolucumab, are given as injections every 2–4 weeks [2]. Evolocumab reduces LDL-C in HoFH patients

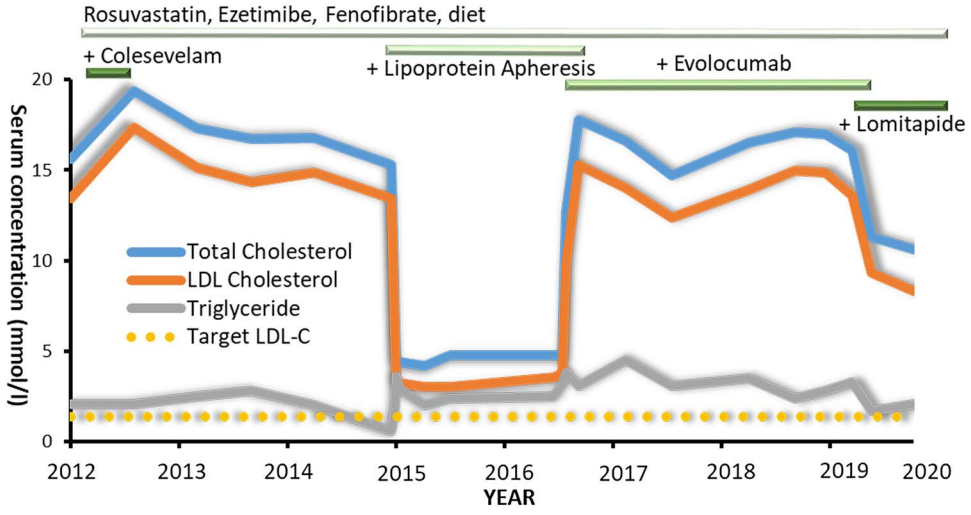

Figure 2: Impact of sequential cholesterol lowering interventions on the patient's lipid profile over time are shown, the ESC target LDL threshold (1.4 mmol/l) is shown in the broken line; to date lipoprotein apheresis achieved the greatest LDL-C reductions (−83% immediately post apheresis), but interval LDL-C were typically 11.8 mmol/l (−35%) equivalent to current therapy which can be managed in the home environment.

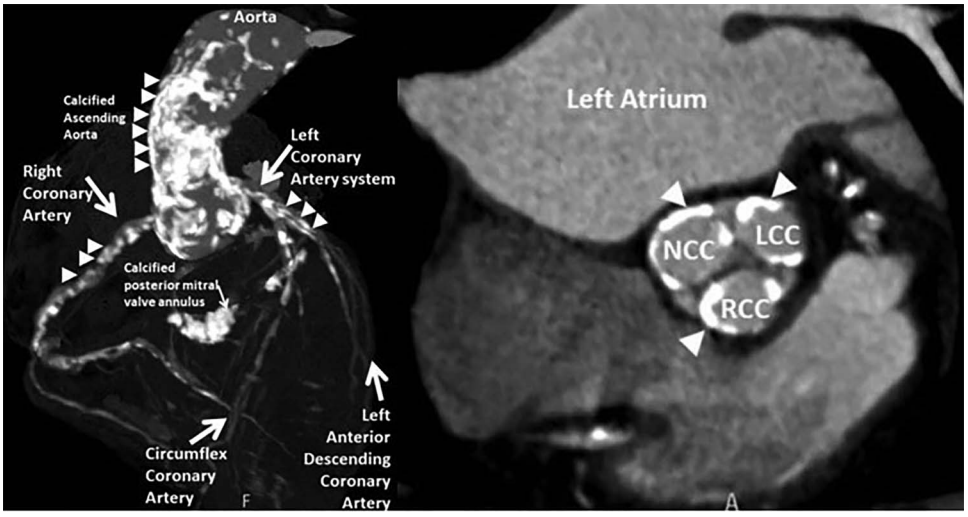

Figure 3: CT assessment of the heart and ascending aorta (left) shows extensive calcification (dense white, arrowheads) of the labeled structures; (right) shows calcification of the three leaflet aortic valve cusps (LCC, left coronary cusp; RCC, right coronary cusp; NCC, non-coronary cusp) causing severe AS.

with or without lipoprotein apheresis (Trial Assessing Long Term USe of PCSK9 Inhibition in Subjects With Genetic LDL Disorders study) accompanied by a reduction in cardiovascular events [5]. However, the addition of PCSK9 inhibition [420 mg injections fortnightly] was ineffective in our patient (~1% LDL reduction). This may be related to the complex spectrum of consequences of the Pro685Leu mutation, which in functional assays include defective processing, accelerated turnover, reduced cell surface expression and impaired LDLR activity [6–9]. Therefore, lomitapide [5 mg ON] was added to the medication regime.

Lomitapide is a microsomal triglyceride transfer protein inhibitor that reduces plasma levels of all APO-B-containing lipoproteins. In our patient, this achieved a 54% reduction in LDL-C after 6 months of treatment (the most recent LDL-C is 8.33 mmol/l). Further dose escalation is planned. Phase II and III, single-arm studies in HoFH show dose-dependent LDL-C reductions between 25 and 51% [10]. An observational study showed a 15% reduction in major adverse cardiovascular events for every 1 mmol/L LDL-C reduction [2]. The monitoring of transaminases is necessary during lomitapide treatment due to increased hepatic fat [2].

Aside from the complexities of this patient's lipid management, it is notable that significant cardiovascular complications have arisen in the absence of symptoms. CVD risk assessment tools developed for the general population do not apply to FH patients as the atherosclerotic burden from long-term exposure to high LDL levels is underestimated [2].

CONCLUSION

HoFH is a very rare severe genetic disorder with cholesterol levels >4-fold normal from birth. Given the increased ACVD risk patients require a multi-agency approach to their care and regular screening for cardiovascular complications.

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Conflict of interest statement. None declared.

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ETHICAL APPROVAL

Standards with respect to publication ethics have been observed.

CONSENT

The patient provides formal written consent to publication of medical photography.

GUARANTOR

Matthew Daniels accepts official responsibility for the overall integrity of the manuscript and attests that all statements in the manuscript are true to his knowledge.

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