Homozygous familial hypercholesterolaemia and treatment by LDL apheresis

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Case report

We report the first known case of true homozygous familial hypercholesterolaemia (FH) in New Zealand and her treatment by LDL-apheresis.

This 13-year-old girl was referred to the lipid clinic by her general practitioner. A recent migrant, she attended requesting statin/ezetimibe combination therapy, as previously prescribed in her native South Africa.

She gave a family history of premature cardiovascular disease and elevated serum lipids. On physical examination marked tendon thickening of both Achilles and the extensor tendons of the hands were noted. Xanthomata were present on the elbows, Figure 1. No arcus corneae were visible. Echocardiography and CT coronary artery scoring indicate a moderately narrowed and calcified proximal aortic root but no coronary calcification.

Figure 1. Xanthomata affecting the extensor tendons of the hands, elbow and Achilles tendons

Biochemical analysis showed an off-treatment total cholesterol of 17.8 mmol/L, triglycerides 1.3 mmol/L and high-density lipoprotein 1.09 mmol/L, giving a calculated low-density lipoprotein (LDL) of 16.1 mmol/L. Lipoprotein(a) was 668 mg/L and apolipoprotein B 2.86 g/L (0.49–1.03).

She was found to be homozygous for the c.681C>G (D206E) mutation on analysis of the LDL-receptor gene, Figure 2.
Rosuvastatin treatment was commenced, and the dose titrated to 60 mg daily in combination with ezetimibe 10 mg daily. This resulted in a reduction in total cholesterol to 10.5 mmol/L and LDL to 9.0 mmol/L. Cholestyramine was added but her cholesterol level remained largely unchanged.

Despite the 37% reduction in LDL achieved with medication, she remained at significant risk of premature cardiovascular disease and hence LDL-apheresis was commenced.

Following her first treatment, the interval mean total cholesterol was 8.3 mmol/L, further treatments are scheduled at fortnightly intervals.

**Discussion**

Familial hypercholesterolaemia is an autosomal codominantly inherited condition characterised by high serum LDL concentrations leading to Fredrickson’s type II hypercholesterolaemia. The raised LDL results in deposition of cholesterol in peripheral tissues and accelerates atherosclerosis.
The monogenic inheritance of FH was first proposed in the mid-1960s by Khachadurian, Brown and Goldstein\(^2\) elucidated the LDL-receptor pathway, followed shortly afterwards by the cloning of the LDL-receptor gene and identification of the first mutation. Over 800 mutations have since been identified.

Five classes of mutation are recognised: class I are null alleles, class II affect protein transport from the ER to the Golgi, class III interfere with LDL binding, class IV hinder clustering in the coated pits and class V impede receptor recycling.

The ‘founder effect’ accounts for the increased frequency of the disease in the Afrikaner, French Canadian, Jewish, Lebanese and Icelandic populations.\(^3\) Three common point mutations, including the c.681C>G (D206E), so called Afrikaner-1 mutation, account for approximately 90% of inherited hypercholesterolaemia in Afrikaners.\(^4\) This class II mutation in exon four leads to the amino acid substitution Asp227Glu and is consistent with severe FH phenotype.

A genetic lipid disorder should be considered in patients with total cholesterol ≥8 mmol/L with or without a family history of premature coronary heart disease; the current New Zealand guidelines\(^5\) recommend referral to a lipid specialist for mutation analysis and cascade screening in these patients.

In our laboratory a combination of direct DNA sequencing and high-resolution melting analysis after PCR amplification are used to screen exons one to 17 for mutations.\(^6\) Multiplex ligation-dependant probe amplification (MLPA) is performed in selected patients to detect large deletions. The APOB gene is also screened for the phenotypically similar Familial Defective Apolipoprotein-B disease (FDB).

Treatment for homozygotes typically involves multiple medications in addition to diet and lifestyle changes. Statins, ezetimibe, resins and niacin may all be employed, and liver transplantation has been advocated. LDL-apheresis, involving extracorporeal filtration and selective removal of LDL, undertaken weekly or biweekly is accepted treatment for homozygous and compound heterozygous FH patients in Europe and the US.

Guidelines for patient selection and treatment goals have been published.\(^7\)–\(^10\) Patients not achieving a 50% reduction in plasma LDL on drug therapy are appropriate for LDL-apheresis and an interval mean total cholesterol of <7 mmol/L, or an acute reduction in total cholesterol of ≥65% have been proposed as treatment targets.

In Christchurch, LDL-apheresis is run in conjunction with the NZ Blood Service and as such could become more widely available. Given the frequency of FH there are likely to be four to five undiagnosed homozygous or compound heterozygous patients in New Zealand who may benefit from this treatment modality.

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