Preventing cardiovascular disease: a review of the effectiveness of identifying the people with familial hypercholesterolaemia in New Zealand

Lauretta A Muir, Peter M George, Andrew D Laurie, Nicola Reid, Lisa Whitehead

Abstract

Aim To identify the diagnostic and treatment rates for familial hypercholesterolaemia (FH) in New Zealand.

Methods The FH data held by Canterbury Health Laboratories and the Canterbury District Health Board lipid clinic was examined to give an indication of the level of identification and treatment of FH in both Canterbury and New Zealand.

Results Between 2004–08, 588 people, out of a possible 10,500 affected people, who presented with a pre-treatment cholesterol \( \geq 8.0 \) mmol/L, lipid stigmata or a strong family history of cardiovascular disease (CVD), were tested for low density lipoprotein (LDLR) and apolipoprotein B (APOB) mutations. Mutations were identified in 76 cases (13%). 353 relatives were screened and 159 (45%) were found to have FH. This data suggests that less than 20% of the affected people in Canterbury have been diagnosed and less than 2.2% nationally.

Conclusion FH diagnostic services in New Zealand appear significantly underdeveloped thereby denying affected people the opportunity of early treatment to reduce the risk of premature cardiovascular events. Cascade screening is shown to be a cost effective and efficient approach to identifying people with FH.

Heterozygous FH is caused by an inherited defect in the function of the low density lipoprotein (LDL) receptor gene that reduces the catabolism of LDL particles, markedly increasing plasma cholesterol levels. It is one of the most common clearly inherited conditions, with prevalence of at least one in 500 in Western populations\(^1\) thereby affecting approximately 10,500 people in New Zealand (NZ).

Untreated FH carries substantial health risks. Those affected will have severely elevated plasma cholesterol levels from the age of two onwards. This confers a greatly increased risk of cardiovascular disease (CVD) in both men and women, with a 100-fold increase in young men.\(^2\) 85% of males and 50% of females with FH will suffer a premature coronary heart disease event before the age of 65 years and as many as 30% will not survive their first myocardial infarction.\(^2\)–\(^3\)

It has been estimated that in the Western world only 20% of cases of FH are detected and less than 10% are being adequately treated.\(^4\) A lack of diagnosis creates a major barrier to the effective prevention of vascular disease,\(^5\) and affects the quality of life and economic and social contributions of affected people and their families. It also causes significant health expenditure such as the costs involved in the provision of cardiac and coronary care, coronary artery surgical procedure and stroke management.
For example, a coronary artery bypass graft surgery can cost up to $NZ50,000 and an angioplasty up to $NZ15,000.

FH can be easily diagnosed and treated giving remarkable health benefits.\(^{3,6–7}\) A provisional diagnosis is made on the basis of the plasma total and LDL cholesterol concentrations, combined with either a clinical examination and family history (together called the phenotype), or a genetic test. Genetic testing is the preferred diagnostic method because it provides an unequivocal diagnosis (genotype).\(^{8}\) A full LDL gene analysis costs approximately $NZ500. With treatment, which carries a cost of approximately $NZ700 per annum, those affected are likely to have the same life expectancy as the general population, especially if treatment is started in early teenage years.\(^{6–8}\)

As first-degree relatives of people who have an LDL receptor mutation have a 50% risk of also having the mutation,\(^9\) the most cost-effective public health/preventive strategy to reduce the impact of FH, is to identify relatives of diagnosed people through cascade screening using clinical and DNA-based diagnostic criteria.\(^{4,10–11}\) This involves working with a diagnosed patient (the index patient or proband) to identify family members, who are contacted and given advice about the condition and offered the opportunity to have mutation analysis.

**Diagnosis and treatment of familial hypercholesterolaemia in New Zealand**

**Method**

National FH data is not currently collected. We therefore review the ability of the NZ public health sector to effectively and efficiently diagnose and treat FH on the basis of laboratory data collected by the Canterbury Health Laboratories (CHL) and cascade screening data held by the Canterbury District Health Board (CDHB) Lipid Clinic. These sites were chosen because CHL is the only laboratory in New Zealand that undertakes testing for FH related mutations and integrates positive results with cascade screening.\(^{12,13}\) The mutation analysis and cascade screening data is compared to the likely number of people affected by FH both in Canterbury and nationally.

**Results**

*Mutation screening*—In the 4-year period between 2004 and 2008 a total of 588 people who presented with a pre-treatment cholesterol ≥8.0 mmol/L, lipid stigmata or a strong family history of CVD, were tested for mutations of the LDL receptor gene; an average of 147 per annum. Mutations were identified in 76 patients (13%) (Table 1).

**Table 1 CDHB FH mutation screening 2004–2008**

<table>
<thead>
<tr>
<th>No of referrals 2004–2008</th>
<th>Identified mutations</th>
<th>Number of relatives screened</th>
<th>Positive familial LDLR mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>588</td>
<td>76 (13%)</td>
<td>353</td>
<td>159 (45%)</td>
</tr>
</tbody>
</table>
Resource levels only permitted minimal genetic testing of patients with low LDL levels but with the appropriate phenotype.

Cascade screening—Patients identified with a mutation were referred to a clinical nurse specialist (CNS) at the CDHB Lipid Clinic for cascade screening. 95 patients with a severe disease phenotype who met the criteria for mutation analysis but did not have an identified mutation, were also referred.

Cascade screening protocols were based on the National Institute for Health and Clinical Excellence, (NICE) guidelines. All referrals provided contact details for their relatives who were sent letters explaining FH, consent forms, and laboratory request forms. Relatives who wanted to be tested returned the consent forms to the clinic and had a blood sample taken at their local laboratory, which was forwarded to CHL. 353 relatives were screened for mutations and 159 (45%) were found to have the familial LDLR mutation (Table 1).

Analysis of cascade screening activities shows that the lack of dedicated resources and the absence of a national database caused up to a 6-month time lag between referral and screening, and minimal follow-up of relatives whose contact details were unknown, did not reply, or lived outside the Canterbury region. There was no follow-up of patients with a severe disease phenotype but no identified mutation, or of children of index patients who reached their teenage years. There was no international follow-up of relatives. The lack of a national database largely prevented the dissemination of information to health professionals regionally and nationally. The position in July 2009 is indicative of service levels over the previous 5 years. (Table 2)

Table 2. Cascade screening in Canterbury, July 2009

<table>
<thead>
<tr>
<th>Category</th>
<th>No of index patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL mutation identified but family cascade screening yet to commence.</td>
<td>8–10</td>
</tr>
<tr>
<td>Clinic waiting for names and contact information of siblings and children from identified index patients.</td>
<td>20–30</td>
</tr>
<tr>
<td>Letters and forms for LDLR mutation Lab screen request sent to children and siblings. Clinic waiting for replies/results. Minimal follow-up.</td>
<td>10</td>
</tr>
<tr>
<td>Partial screening of siblings and children—prioritised by age and history. Parents advised to have children under 15 screened by the time they are 15 years of age.</td>
<td>90–111</td>
</tr>
<tr>
<td>Local extended family follow-up.</td>
<td>8–10</td>
</tr>
<tr>
<td>National or international follow-up.</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
</tr>
</tbody>
</table>

In spite of these limitations, the rate of diagnosis in relatives who agreed to mutation screening (45%) is consistent with international evidence that indicates that cascade screening of first-degree relatives is a cost-effective approach to diagnosis. Rates of diagnosis—The Canterbury region has a population of approximately 600,000, or about 13% of the national population. Of the 10,500 people that are
likely to be affected nationwide, approximately 1,200 are expected to be in Canterbury with the remainder distributed throughout the country. Referrals generally came from the CDHB Lipid Clinic and approximately 50 referrals were from outside Canterbury.

The number of genetic screens undertaken between 2004 and 2008 suggests that less than 20% of the affected individuals in Canterbury have been diagnosed and, at current rates of identification it is likely to take up to 21 years to detect all FH affected people in the region.

The situation appears worse nationally. Referrals to CHL for mutation screening and follow-up of members of the extended family of identified patients suggest that possibly less than 2.2% of people in NZ with FH have been identified. This implies that up to 10,000 affected people have not been diagnosed and are at risk of developing premature CVD.

**Discussion**

A number of variables affect the ability of the health sector to diagnose FH and effectively prevent the onset of vascular disease in this group of people. The aetiology of FH and the steps involved in diagnosis, means that it does not fit neatly into a specific service or sector.

Diagnosis and treatment involves the specialist expertise of various health care providers in areas as diverse as endocrinology, chemical pathology, molecular genetics, lipid clinics, cardiology, radiology, paediatrics, dietetics, genetic counselling etc., with the locus of care spanning secondary and tertiary hospital settings, publicly and privately owned laboratories, private specialist clinics and general practices.

The patient spread is across all age groups. Cascade screening is unlikely to be carried out as part of a normal patient consultation because it is time consuming and requires expertise in both FH and genetic screening. National guidelines for reducing the risk of CVD that recommend population screening of men over 45 years and women over 55 years are unlikely to assist in diagnosis until after vascular disease is well advanced.

Consistent with the findings of Grey et al (2008), there are likely to be diagnosed and undiagnosed cases of FH in primary care that are not known to secondary care and that significant potential exists to identify new cases of FH in primary care who could act as new index cases for a family screening programme.

**Conclusion**

FH is a clearly defined condition with a poor prognosis. Yet it is relatively easy to diagnose and treat resulting in remarkable improvements in health outcomes. FH diagnostic services in New Zealand appear significantly underdeveloped thereby denying affected people the opportunity of early treatment to reduce the risk of premature cardiovascular events. Cascade screening is a cost effective and efficient approach to diagnosis but New Zealand lacks the necessary supporting infrastructure.

The development of an integrated, national model of care that is widely disseminated and clearly understood by primary, secondary, and tertiary clinicians is
likely to significantly reduce the risk of CVD, reduce sector costs, and improve health outcomes.

Competing interests: None known.

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