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Detecting familial hypercholesterolaemia in the community: Impact of a telephone call from a chemical pathologist to the requesting general practitioner

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ABSTRACT

Objective: To determine whether a telephone call from a chemical pathologist to the requesting general practitioner (GP) of individuals at high risk of familial hypercholesterolaemia (FH) increases specialist referral and detection of FH.
Method: Individuals with an LDL-cholesterol ≥6.5 mmol/L without secondary causes were identified from a community laboratory; 100 cases and 96 historical controls.
All laboratory reports (cases and controls) received interpretative comments highlighting FH. In addition, the cases' GPs received a telephone call from the chemical pathologist to highlight their patient's risk of FH and suggest specialist referral, whereas with the controls' GPs were not telephoned.
Results: After 12 months follow-up, 27 (27%) cases were referred to clinic compared with 4 (4%) controls ($p < 0.0001$). 25 cases were reviewed at clinic, 12 (48%) had definite FH and 18 (72%) had probable or definite FH according to the Dutch Lipid Clinic Network Criteria, 2 cases did not attend their clinic appointments. Genetic testing was performed in 23 individuals: 7 (30%) had pathogenic FH mutations. Genotypic cascade screening of 4 kindreds from the intervention group detected an additional 7 individuals with FH and excluded 5 mutation-negative family members.
Conclusions: A telephone call from a chemical pathologist to the requesting GP of patients at high risk of FH was associated with significantly higher rates of FH detection and specialist referral. Over 70% of individuals with an LDL-cholesterol ≥6.5 mmol/L were diagnosed with FH. However, further investigation is required to improve the relatively low referral rate.

1. Introduction

Familial hypercholesterolaemia (FH) is a co-dominantly inherited condition characterised by elevated low-density lipoprotein cholesterol (LDL-cholesterol) and premature atherosclerotic cardiovascular disease. However, worldwide the majority of individuals with FH are currently undiagnosed, and those who are diagnosed, are often undertreated [1,2]. Most countries do not have a systematic screening program despite FH fulfilling the World Health Organization criteria for disease screening [1–3]. Detecting individuals with FH early is important, as statin therapy significantly reduces ischaemic heart disease and mortality in FH [4,5].

Community laboratories are well placed to opportunistically screen for FH, as they measure large numbers of lipid profiles [6,7]. However, most individuals identified at high risk of FH by the community laboratory are not currently referred to lipid specialists [8], and the most effective method of highlighting individuals at high risk of FH to their requesting general practitioner (GP) remains

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to be elucidated. We sought to determine the impact of a telephone call from the chemical pathologist to the requesting GP of individuals at high risk of FH (LDL-cholesterol ≥6.5 mmol/L) on FH detection and specialist referral rates.

2. Methods

This case–historical control study consisted of individuals selected on the basis of an LDL-cholesterol ≥6.5 mmol/L measured by St John of God Pathology (SJGP), a private community laboratory in Western Australia, if the lipid profile was requested by a GP. This LDL-cholesterol threshold has previously been shown to identify individuals at high risk of FH [9,10]. Individuals were excluded if they had a potential secondary cause of hypercholesterolaemia [hypothyroidism (TSH >4.0 mU/L), mixed hyperlipidaemia (triglyceride > 4.0 mmol/L), nephrotic syndrome (proteinuria >3 g/L and serum albumin <30 g/L), or cholestasis (alkaline phosphatase (ALP) > 135 U/L and γ glutamyltransferase (GGT) > 55 U/L in males or >38 U/L in females)] identifiable within 30 days of the LDL-cholesterol result from SJGP.

The intervention group, identified between the 1st of November 2010 and the 6th of October 2011, consisted of the first 100 individuals meeting the above selection criteria whose GP answered the telephone call from one of the three chemical pathologists at SJGP. During this call the chemical pathologist informed the GP that the patient was at high risk of FH, provided information on the mode of inheritance and increased premature cardiovascular disease (CVD) risk associated with FH, and suggested referral to the regional lipid disorders clinic. A handout on FH specifically designed for health professionals was also offered. The control group, selected between the 23rd of June and the 19th of October 2010, consisted of 96 individuals with the same inclusion and exclusion criteria as above, except their GP did not receive a telephone call from the chemical pathologist. Individuals in both the intervention and control groups received interpretative comments with the lipid results highlighting the patient is at risk of FH, as previously described [8].

To determine the impact the telephone call had on FH detection, the number of referrals to the regional lipid disorders clinic was compared over the 12 months following the LDL-cholesterol being reported for each individual in the intervention and control groups. This was performed by manually comparing the study and lipid disorders clinic databases. In order to capture data on individuals who may have been reviewed by a private specialist, the regional cardiovascular genetics laboratory database was screened to determine if genetic testing had been performed on any of these individuals.

The impact on FH detection was ascertained by reviewing the outcome of the specialist consultation for individuals referred to the lipid disorders clinic by manually searching the lipid disorders clinic database, and by reviewing the cardiovascular genetics database for the individuals not referred to the clinic. Genetic testing was performed as part of routine care as previously described [11].

Statistical analysis was performed using Microsoft Excel 2003, STATA, StataCorp. 2011, Stata Statistical Software, release 13. Two-tailed Chi-squared or Fisher's exact tests were used to compare categorical data, and unpaired two-tailed *t*-tests were used for continuous data. This study was approved by the Royal Perth Hospital Human Research Ethics Committee (EC 2011/069). The investigation and management of all individuals referred to the lipid disorders clinic was performed as part of routine clinical service, and was not affected by this study.

3. Results

During the case selection period, 94,799 LDL-cholesterol results were issued by SJGP; with 164 LDL-cholesterol results ≥6.5 mmol/L. In order to contact the requesting GP for the 100 individuals in the intervention group, a chemical pathologist made 158 telephone calls about 113 individuals; 13 GPs could not be contacted. There were 82 different GPs for the 100 individuals in the intervention group; their mean LDL-cholesterol was 7.1 ± 0.7 mmol/L, (Table 1). There were 83 different GP requestors for the control group; their mean was 7.1 ± 0.8 mmol/L. The control group has been previously described [8]. The cases (49.3 years) were younger than controls (53.7 years), but there were no other significant differences in demographics.

Twenty seven (27%) individuals in the intervention group were referred to the lipid disorders clinic during the 12 months follow up after the telephone call. One was already known to the clinic (*LDLR* mutation-positive FH) and two failed to attend their appointments, thus 25 individuals underwent specialist review (Table 2). No patients were referred for FH genetic testing from private specialists over this time.

Using the Dutch Lipid Clinic Network Criteria (DLCNC) to assess the clinical likelihood of FH in the 25 individuals, 18 (72%) were clinically diagnosed with FH (probable 6 (24%) or definite 12 (48%) FH). Genetic testing was performed in 23 individuals, seven (30%) of whom had identifiable FH-causing mutations. Four individuals from the control group were referred to the lipid disorders clinic in the 12 months following selection. All four controls were clinically diagnosed with FH: two probable and two definite FH. Genetic testing was performed on all four, the two clinically definite FH individuals had identifiable FH-causing mutations, and the two clinically probable individuals did not.

The specialist referral rate was significantly greater in the intervention group than in the control group (27% vs. 4%; $p < 0.0001$). Genotypic cascade screening has been performed in 12 family members from four mutation-positive FH individuals in the intervention group to date; seven were confirmed carry the FH mutation and five did not.

In general, the phone calls made by the chemical pathologists were well received and deemed to be useful by the GPs; 82% were positive with those GPs engaging in discussion with the chemical pathologists with respect to the clinical aspects of the case, 12% were neutral, and 4% negative, citing clinic time pressures.

4. Discussion

This case–historical control study demonstrates that a telephone call from a chemical pathologist to the requesting GP of a patient at high risk of FH significantly improves FH detection and specialist referral rates in addition to interpretative comments. These findings also confirm the important role that a community

Table 1
Subject characteristics and FH detection rates.

Characteristics	Controls	Cases	Significance (*p*)
Number	96	100	
Females, n	68	57	0.05
Age (years), mean ± SD, [range]	53.7 ± 10.7 [26–74]	49.3 ± 12.4 [15–76]	0.009
LDL-cholesterol (mmol/L), mean ± SD, [range]	7.1 ± 0.8 [6.5–11.2]	7.1 ± 0.7 [6.5–9.5]	1.0
Referred to specialist, n (%)	4 (4%)	27 (27%)	<0.0001
Clinical FH (probable or definite) n (%)	4 (4%)	18 (18%)	0.003
Probable FH, n (% of clinically assessed)	2 (50%)	6 (24%)	0.28
Definite FH, n (% of clinically assessed)	2 (50%)	12 (48%)	0.01#
Mutation identified, n (% of genetically tested)	2 (50%)	7 (30%)	0.58

Continuous variables were compared with two-tailed unpaired *t*-tests.
Categorical data were compared with either two-tailed Fisher's exact or χ^2 tests.
#*p* refers to the difference in absolute numbers, not proportion.