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Frequency of familial hypercholesterolemia in patients with early-onset coronary artery disease admitted to a coronary care unit

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BACKGROUND: Familial hypercholesterolemia (FH) is the most common dominantly inherited cause of premature coronary artery disease (CAD). However, the diagnosis of FH in patients who have premature CAD in hospital settings is under-recognized, this also represents a missed opportunity for screening their close family members and implementing primary prevention.

OBJECTIVE: To investigate the point prevalence of FH in a coronary care unit (CCU) among patients with early-onset CAD.

METHODS: The prevalence of FH, based on modified phenotypic Dutch Lipid Clinic Network Criteria, and the spectrum of associated CAD risk factors, were investigated in a CCU setting. Data were collected on 175 coronary care patients with onset of CAD at age <60 years.

RESULTS: The prevalence of probable/definite FH was 14.3% (95% confidence interval, 9.0%–19.5%); 46.3% of the patients gave a family history of premature CAD and 20.6% had an untreated low-density lipoprotein cholesterol >5.0 mmol/L. Diabetes, hypertension, obesity, and smoking were common and equally prevalent in patients with and without FH.

CONCLUSIONS: FH is relatively frequent among patients with a history of early-onset CAD in the CCU. Every effort should be made to detect FH in these patients and to initiate cascade testing of available family members to prevent the development of CAD in those who may be unaware that they also have the condition.

Introduction

Familial hypercholesterolemia (FH) is a relatively common dominantly inherited condition resulting in markedly elevated plasma levels of low-density lipoprotein (LDL)

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cholesterol and premature coronary artery disease (CAD). The risk of CAD in FH is preventable or reversible through early detection and treatment of hypercholesterolemia.[1] FH remains underdetected and undertreated in most countries.[2,3]

International guidelines have accordingly recommended several screening strategies for FH. An important one is the detection in coronary care units (CCUs) of potential index cases who then trigger cascade testing for the condition in close family members.[2–5] The value of this integrated approach has not been adequately recognized, and, as a consequence, a key opportunity for detecting FH has not been embedded in routine clinical care.

We therefore investigated the prevalence of FH using a modified and simplified version of the Dutch Lipid Clinic Network Criteria (DLCNC) among patients with early-onset CAD in a CCU. We also assessed the spectrum of modifiable non-cholesterol risk factors in these patients.

Methods

We studied 175 consecutively available patients, over 2 periods of 12 weeks each in 2011 and 2013 admitted to the CCU of the Royal Perth Hospital, Perth, Western Australia. Patients had to have been admitted with a current or prior history of CAD (acute coronary syndrome, coronary revascularization, or angina) at an age <60 years. Clinical data were collected prospectively by a nurse from medical records and by direct interview of patients.

All patients were assessed using the modified DLCNC[2]: premature family history of CAD (at age <55 years for men and <60 years for women; 1 point); personal history of CAD (2 points), personal history of stroke (1 point); and plasma LDL cholesterol >8.5 mmol/L (8 points), LDL cholesterol 6.5–8.4 (5 points), LDL cholesterol 5–6.4 mmol/L (3 points), LDL cholesterol 4–4.9 mmol/L (1 point). Individuals on statins had their plasma LDL cholesterol conservatively adjusted by a correction factor that depends on the dose and potency of specific statins to estimate pretreatment levels; the mean correction factor was 2.0, consistent with adjustments in the literature.[6] FH was defined as the numerical sum to each of the previously mentioned criteria: definite, score >8; probable, score 6–8; possible, score 3–5; and unlikely, score <3. In the present study, phenotypic FH was defined as a score >5 (probable/definite FH). Cardiovascular risk factors, such as smoking, diabetes, hypertension, and obesity, were obtained from the medical history in the hospital records.

We also assessed the prevalence of individuals with a family history of premature CAD, an LDL cholesterol >5.5 mmol/L, >5.0 mmol/L, and >4.5 mmol/L, and the prevalence of meeting both the family history and aforementioned LDL cholesterol criteria. We have evidence that an LDL cholesterol >5.0 mmol/L is predictive of a pathogenic mutation causative of FH with high sensitivity (>85%) and reasonable specificity (>60%), and this criterion combined with a family history of early-onset CAD has also been used to diagnose FH.[7]

Fasting blood samples were collected in which a plasma lipid profile was assayed using standard enzymatic methods, with LDL cholesterol calculated by the Friedewald equation. Patients with secondary hypercholesterolemia (hypothyroidism and proteinuria) were excluded. In patients with triglyceride >4.5 mmol/L, LDL cholesterol was directly measured. Data were collated using Microsoft Access and Excel 2010 and analyzed using STATA 12 (StataCorp, 2011, Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Data were compared using unpaired *t* tests and chi-square tests. Concordance rates and kappa statistics were also used to compare diagnostic criteria for FH. The study was approved by the Clinical Audit and Safety Unit at Royal Perth Hospital (QI Registration No: QI 120124-1).

Results

The patients were middle-aged (50.3 ± 7.1 years), 81% were men, 92% Caucasian, and 28% were on statin therapy at first review; untreated LDL cholesterol level was on average 4.13 ± 1.41 mmol/L. The average DLCNC score was 3.6 ± 2.0, and 21% of patients had type II diabetes, 46% hypertension, and 12% obesity. Thirty-five percent of patients were current smokers and 18% ex-smokers.

Table 1 shows the prevalence of FH, defined according to different criteria. The point prevalence of probable FH was 12.0% and definite FH 2.3%, with the combined prevalence of probable/definite FH being 14.3% (95% confidence interval [CI], 9.0–19.5); over half of patients had possible FH. Excluding 6.3% of patients with angina pectoris alone, the prevalence of probable/definite FH was 15.2% (95% CI, 9.7–20.8). The prevalence estimates for FH did not differ significantly between the 2 sampling periods. Overall, 46.3% of the patients had a family history of premature CAD, but only 12.0% and 20.6% had an untreated LDL cholesterol >5.5 mmol/L and >5.0 mmol/L, respectively; 10.9% had both an untreated LDL cholesterol >5.0 mmol/L and a family history of premature CAD, a criterion which was significantly concordant with a DLCNC >5 (kappa = 0.79; $P < .001$).

Probable/definite FH was more common in those with CAD onset aged <50 years compared with those aged 50 to 60 years (15.1% vs 13.3%) and more common in women than men (20.6% vs 12.8%), but the differences were not statistically significant. The prevalences of FH according to the criteria shown in Table 1 were not significantly influenced by excluding patients with hypertriglyceridemia (defined as a triglyceride concentration >2.5 mmol/L or >1.8 mmol/L). A pathogenic mutation causative of FH[8] was found in 3 of 6 (50%) patients with phenotypic FH