European Journal of Internal Medicine 26 (2015) 127–130

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Prevalence of DNA-confirmed familial hypercholesterolaemia in young patients with myocardial infarction☆,☆☆,★

David S. Wald [a,b,*], Fatima A. Bangash [a], Jonathan P. Bestwick [a]

[a] Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom
[b] London Chest Hospital, Bonner Road, London E2 9JX, United Kingdom

ARTICLE INFO

Article history:
Received 10 September 2014
Received in revised form 1 December 2014
Accepted 25 January 2015
Available online 11 February 2015

Keywords:
Familial Hypercholesterolaemia
Premature
Myocardial infarction

ABSTRACT

Purpose: To report the prevalence of DNA-confirmed Familial Hypercholesterolaemia (FH) in young patients with acute myocardial infarction, the relative contribution of smoking and diabetes and to compare these rates with those in the general population.
Methods: A pilot clinical service was established to diagnose FH in young patients (≤50 years) with myocardial infarction at a London hospital. Over 23 months, 231 such patients, underwent testing for 48 common FH-mutations and whole exon *LDLR* gene deletions and duplications. Patients with total cholesterol levels ≥7.0 mmol/L, additionally, underwent full sequencing of the *LDLR* gene. Smoking and diabetes history were recorded. The prevalence of FH, smoking and diabetes were determined and compared with the prevalence in age and sex matched controls from published surveys.
Results: The prevalence of DNA-confirmed FH was 1.3% (95% confidence interval 0.3%–3.8%) compared with 0.2% (0.17%–0.23%) in the general population ($p = 0.012$). Observed prevalence rates for smoking and diabetes were 57% (50.3%–63.6%) and 13.4% (9.2%–18.6%) respectively in patients, compared with expected rates of 25% (23.9%–26.2%) and 4.6% (4.1%–5.2%) in the general population ($p < 0.001$ for both comparisons).
Conclusion: FH is an important cause of premature myocardial infarction but it accounts for only a small proportion of all such events. The endemic risk factors, smoking and diabetes, far exceed FH in patients with acute myocardial infarction aged 50 or less. Consideration should be given to extending the use of statins and blood pressure drugs to a younger group of smokers and diabetics, who are excluded from treatment by conventional prevention strategies.

1. Introduction

Acute myocardial infarction in young individuals (≤50 years) causes about 60,000 deaths in the European Union and the USA each year [1]. With the decline in smoking and total cholesterol over the past decade, attention has focussed on inherited causes of coronary heart disease (CHD) to explain these early events, the most common of which is the autosomal dominant disorder Familial Hypercholesterolaemia (FH). An estimated 1 in 500 people are affected and have a high risk of developing CHD at a young age [2]. Early identification of affected cases is important because statins, which reduce serum cholesterol, substantially reduce risk [3].

In 2008 the UK's National Institute for Health and Care Excellence (NICE) recommended screening for FH by testing the first degree relatives of affected individuals (half of whom would be affected), but acknowledged that fewer than half of all cases in the population would be identified in this way, because the method is self-limiting [4,5]. Once all relatives of an index case have been tested, the method cannot proceed further unless some separate method is used to identify new unrelated index cases. Systematic searching for FH-causing mutations, the gold-standard test for FH, among patients with premature myocardial infarction has been proposed as a means of doing this [4].

In 2011 a pilot clinical service was set up at a London cardiac centre to identify FH among young patients with acute myocardial infarction. The service was evaluated in 2013. We report the prevalence of DNA-confirmed FH, smoking and diabetes, in patients with premature myocardial infarction (≤50 years of age) and compare this with the prevalence in the general population.

2. Methods

Patients aged 50 years or less, with ST elevation myocardial infarction or Non-ST elevation myocardial infarction were identified by a

☆ Service evaluation.
☆☆ Funding source: Service enhancement grant from Barts and The London Charity.
★ All authors had access to the data and a role in writing the manuscript.
* Corresponding author at: Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ, United Kingdom. Tel.: +44 020 7882 6298; fax: +44 020 7882 6270.
E-mail addresses: d.s.wald@qmul.ac.uk (D.S. Wald), f.bangash@qmul.ac.uk (F.A. Bangash), j.p.bestwick@qmul.ac.uk (J.P. Bestwick).

http://dx.doi.org/10.1016/j.ejim.2015.01.014
0953-6205/

pharmacist or doctor on cardiac care ward rounds and offered testing for FH by DNA analysis. It was explained that identification of an FH-causing mutation in the patient may help identify family members with FH so treatment could be offered to them to prevent a myocardial infarction and all patients were routinely offered testing on this basis. Non-fasting blood for serum cholesterol measurement was collected from patients on admission to hospital. Whole blood for DNA analysis was collected from patients who agreed to being tested, usually the day after admission, regardless of their cholesterol level. DNA was extracted by standard methodology [6] and analysed for 48 common mutations known to cause FH in the UK, using custom Taqman® SNP genotyping assays (Applied Biosystems™ with the BioMark™ Fluidigm HD system [7]) and for whole exon deletions/duplications of the LDLR gene using Multiplex ligation-dependent probe amplification (MLPA) (Supplementary Table 1) [8].

DNA from patients with a total cholesterol ≥7.0 mmol/L (271 mg/dL), in whom no mutation was found using the FH48 panel, was further analysed by bidirectional Sanger sequencing (ABI BigDye Terminator sequencing Kit v.3/ABI3730 capillary sequence analysis; Applied Biosystems™) of the entire *LDLR* gene coding region and intron/exon boundaries, to identify less common mutations, among those with high total cholesterol. Patients found to be positive for FH were treated according to NICE guidelines [4] and were offered cascade testing of their family members, with testing for the mutation found in the affected proband. The service development was funded for 2 years after which time an audit was conducted and the service evaluated to assess its feasibility, acceptability, and the prevalence of DNA — determined FH among the patients tested during that period. As it was a service evaluation, research ethics approval was not required [9].

The prevalence of FH in young patients with myocardial infarction was calculated as the number of patients with DNA-confirmed FH divided by the total number of patients tested together with Poisson 95% confidence intervals [10] and compared with the prevalence of definite FH in the general population using data from a large Danish general population cohort (69,016 participants) who underwent DNA analysis for FH-causing mutations [11]. Individuals in this study were randomly selected from the National Danish Civil Registration System, and were tested for the most common FH-causing mutations in Denmark, regardless of cholesterol levels (median age 58, 45% male and 11% taking statin treatment).

The prevalence of smoking and diabetes in our sample was also determined and compared with the age and gender matched prevalence in the general population using data from the Health Survey for England, an annual survey which, in 2012, included a random sample of 6700 individuals [12]. Prevalence rates were calculated together with binomial 95% confidence intervals [13]. The frequencies of FH, smoking and diabetes were compared between young patients with myocardial infarction and the general population using Fisher's exact test. Statistical significance was taken as $p < 0.05$. Stata version 12 (Statacorp, College Station, Texas) was used for all analyses.

Table 1
Baseline characteristics of 231 patients with acute myocardial infarction aged 50 or less.

Characteristic	Number of patients (%)
Diagnosis	
NSTEMI	64 (28)
STEMI	167 (72)
Male	199 (86)
Age, years*	45 (41–48)
Family history of CHD† under age 50	57 (26)
Smoker	
Yes	129 (57)
Former	24 (11)
Never	72 (32)
Diabetic	30 (13)
Previously taking statins	57 (25)
Total cholesterol (mmol/L)*‡	5.5 (4.5–6.3)

* Median, (interquartile range).
† CHD, coronary heart disease.
‡ 1 mmol/L total cholesterol = 38.7 mg/dL.

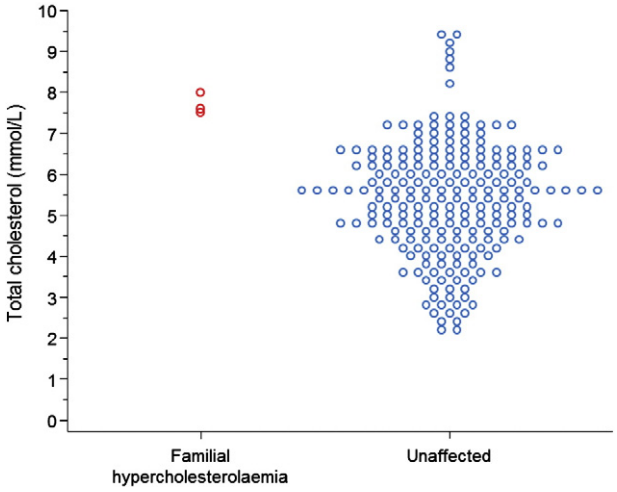

Fig. 1. Total cholesterol levels in patients with and without DNA-determined FH (1 mmol/L = 38.7 mg/dL).

3. Results

Between June 2011 and April 2013, 3076 patients with acute myocardial infarction were admitted to hospital and 474 were aged 50 or less. Of these, 240 underwent DNA analysis for FH (66 declined testing, 43 did not speak English, 35 were too unwell, and 90 were not offered testing because they were weekend admissions). In nine patients the DNA analysis failed leaving 231 for analysis. Table 1 shows their baseline characteristics.

Three out of the 231 patients with myocardial infarction were found to have an *LDLR* gene mutation (c.2289G > T, c.2416dupG and c.190 + 4A > T), a prevalence of 1.3% (95% confidence interval 0.3%–3.8%). The 3 affected cases were aged 26, 47 and 50 years and were not known to have FH or be on statin treatment prior to admission. Fig. 1 shows the total cholesterol concentrations (7.5 mmol/L (290 mg/dL), 7.6 mmol/L (294 mg/dL) and 8.0 mmol/L (309 mg/dL) respectively) in the 3 cases and in unaffected patients.

Table 2 compares the observed prevalence of FH, smoking and diabetes among the 231 young patients with myocardial infarction, with the expected prevalence in the general population, based on published estimates. The absolute and relative differences in prevalence of FH, smoking and diabetes were 1.1%, 32%, 8.8% and 6.5, 2.3 and 2.9 respectively.

Table 2
Prevalence of FH, smoking and diabetes in patients with myocardial infarction (aged 50 or less) compared with the general population.

Risk factor	Observed (95% CI)	Expected (95% CI)	Prevalence ratio (95% CI)	p-value
FH	1.3% (0.3%–3.8%)	0.20% (0.17%–0.23%)†	6.5 (2.1–20.4)	0.012
Smoking	57.1% (50.3%–63.6%)	25.1% (23.9%–26.2%)*	2.3 (2.9–2.6)	<0.001
Diabetes	13.4% (9.2%–18.6%)	4.6% (4.1%–5.2%)*	2.9 (2.0–4.1)	<0.001

95% CI (95% confidence interval).
† Benn et al. 2012 [11].
* Health Survey for England 2012 [12].