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Heterozygous familial hypercholesterolaemia in specialist centres in South Africa, Australia and Brazil: Importance of early detection and lifestyle advice

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ABSTRACT

Background and aims: Familial hypercholesterolaemia (FH) is the commonest monogenic disorder that accelerates atherosclerotic cardiovascular disease. We compared and contrasted the characteristics of patients from three specialist centres in the southern hemisphere.
Methods: Adult index-cases with molecularly diagnosed heterozygous FH attending specialist lipid centres in Cape Town, Perth and São Paulo were studied. Myocardial infarction, revascularisation, hypertension, diabetes, smoking and lipid-lowering treatment were recorded at the time of diagnosis and compared across the three centres.
Results: The spectrum of genetic variants causative of FH was significantly different in patients attending the centres in South Africa compared with Australia and Brazil. Hypertension and diabetes were more prevalent in Brazilian and Australian patients, than in South African patients, but the frequency of smoking was significantly greater in South Africa than the other two centres ($p<0.01$). Age, male sex and smoking were significant independent predictors of coronary artery disease (CAD) in all three countries ($p<0.05$).
Conclusions: Patients with FH in three specialist centres in the southern hemisphere exhibit a high prevalence of non-cholesterol cardiovascular disease risk factors. Older age, male sex and smoking were more common among subjects with CAD. In all three countries, there should be vigorous programmes for the control of risk factors beyond good control of hypercholesterolaemia among patients with FH. Promotion of a healthy lifestyle, especially anti-smoking advice, is of paramount importance.

1. Introduction

Familial hypercholesterolaemia (FH) is characterised by elevated low-density lipoprotein cholesterol (LDL-C) levels owing to mutations in genes involved in the low-density lipoprotein receptor (LDLR) pathway. Heterozygous FH (heFH) is the commonest monogenic lipid disorder that accelerates atherosclerotic cardiovascular disease (CVD). The relatively high population frequency estimates of 1:250 to 1:300 [1–5] implies that FH must be viewed as a public health problem throughout the world, noting also that

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the majority of people with FH are undiagnosed and/or undertreated [6]. Beyond LDL-C, lifestyle and other risk factors also need to be addressed in the care of patients with FH [7].

Most reports in the medical literature on the detection, management and treatment of FH have been focused on the northern hemisphere [8], with fewer reports on the southern hemisphere [9]. International comparisons among patients attending specialist centres remain outstanding. As part of the "Ten Countries Study" [10], we took the opportunity to compare and contrast the clinical characteristics, CVD risk factors, genetic variants, and the corresponding associations with the prevalence of coronary artery disease (CAD) in molecularly confirmed adult index cases with heFH attending three specialist centres in South Africa, Australia and Brazil. We wanted to explore whether apart from differences in FH genetic variants, patients attending the different centres have variable prevalence and severity of non-cholesterol risk factors that could impact on the risk of CAD.

2. Patients and methods

We obtained data from hospital records and clinic databases on all index patients (first to be diagnosed in a family) aged 18 years or more and known to have a pathogenic mutation affecting the LDLR pathway (*LDLR*, *APOB* and *PCSK9* genes). Data from three specialist centres in Cape Town (South Africa) [11], Perth (Australia) [12] and São Paulo (Brazil) [13] were collated for the study between 1990 (post-statin) to 2017. All three centres followed a consistent service delivery model of care over this time period. Details of the services provided, including genetic testing, and the characteristics of patients attending these centres have been published elsewhere [11–13]. Patients with homozygous and compound heFH patients were excluded owing to the inordinately high prevalence of this type of FH in South Africa as a consequence of a founder effect; details of the homozygous FH cohort have been reported elsewhere [14]. Local ethics committee approval was obtained and informed written consent was obtained from all patients regarding the use of de-identified information.

Clinical characteristics such as history of CAD (defined as a myocardial infarction and/or coronary revascularisation), hypertension, diabetes, tendon xanthomata (assessed by clinician), smoking and lipid-lowering treatments were abstracted from hospital records at the time of FH diagnosis. Premature CAD was defined as <55 years for men and <60 years for women. Hypertension and diabetes were diagnosed according to local standard criteria. Smoking was defined as current or previous smoking. The highest pre-treatment LDL-C was also recorded. If an untreated LDL-C was not available, a correction factor was applied to estimate the pre-treatment LDL-C [15–17]. Laboratory methodology for lipid and genetic testing have been previously described [11–13,18].

Data were collected using Microsoft Excel and Access 2013. Databases were aligned, amalgamated and analysed using STATA 13.1 (College Station, TX: StataCorp LP). Continuous variables were described as mean ± standard deviation and categorical variables were expressed as proportions. The characteristics of the patients from Australia and Brazil were compared with those from South Africa, as the reference group. Group differences were investigated using regression analyses. Differences in patients with and without CAD were assessed by paired *t*-tests and chi-square tests. Univariate and multivariate logistic regression analyses were performed to predict the probability of CAD. We restricted the selection of variables in the multivariate model to only those that were significantly associated with CAD in univariate analyses. Significance was defined at 5%.

3. Results

Table 1 summarises the clinical characteristics of the 875 adult index cases with molecularly defined heFH from South Africa (n = 353), Australia (n = 266) and Brazil (n = 256). FH patients from South Africa were younger at presentation to the specialist clinic compared with patients from Australia and Brazil ($p<0.001$). Diagnosis was relatively delayed in Brazil at a mean age of 50.4 ± 14.1 years; this is almost a decade later than patients from South Africa at 41.0 ± 13.3 years and 5 years later than patients from Australia at 45.5 ± 13.8 years.

Modifiable CVD risk factors, such as hypertension and diabetes, were more prevalent in patients from Brazil and Australia compared with those from South Africa ($p<0.01$), however, smoking rates were significantly higher in South African patients ($p<0.01$).

Despite the earlier diagnosis, rates of coronary events were particularly high in South Africa with 21.0% having experienced a myocardial infarction and 18.4% having undergone a revascularisation procedure. Among those with CAD, age of first coronary event was also earlier in South Africa compared with Australia and

Table 1
Clinical characteristics of adult index cases with molecularly defined heterozygous familial hypercholesterolaemia from South Africa, Australia and Brazil.

	All	South Africa	Australia	Brazil
	n = 875	n = 353	n = 266	n = 256
Age (years)	45.1 ± 14.2	41.0 ± 13.3	45.5 ± 13.8[a]	50.4 ± 14.1[a]
Sex (% male)	45.6	51.3	41.4[b]	42.2[b]
Myocardial infarction (%)	16.5	21.0	9.8[a]	17.2
Coronary revascularisation (%)	16.8	18.4	18.1	13.3
CAD (%)	24.6	28.6	20.3[c]	23.1
Premature CAD (%)	22.9	26.4	19.2[c]	21.9
Age at first event (years)	43.3 ± 10.8	39.3 ± 10.5	46.8 ± 9.5[a]	46.7 ± 10.5[a]
History of hypertension (%)	20.5	11.9	22.9[a]	29.7[a]
History of diabetes (%)	5.3	0.6	5.3[b]	11.7[a]
History of smoking (%)	43.2	52.4	41.0[b]	32.8[a]
Tendon xanthomata (%)	43.0	76.2	31.2[a]	10.7[a†]
Pre-treatment LDL-C (mmol/L)	7.5 ± 1.9	7.4 ± 1.9	8.0 ± 1.9[a]	7.0 ± 2.0[b]
HDL-C (mmol/L)	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.4[a]	1.2 ± 0.3
Non-HDL-C (mmol/L)	8.1 ± 2.0	8.1 ± 1.9	8.4 ± 1.9	7.8 ± 2.0
Lipid-lowering treatment (%)	59.2	31.7	74.4[a]	81.3[a]

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as proportions (%). Significantly different from South Africa (reference group); [a]$p<0.001$, [b]$p<0.01$, [c]$p<0.05$. †16% of the cohort from Brazil had no comment about tendon xanthomata.
CAD: coronary artery disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.