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Predictors of cardiovascular events after one year of molecular screening for Familial hypercholesterolemia

Pãmela R.S. Silva [a, *], Cinthia E. Jannes [a], Julia D.C. Marsiglia [a], Jose E. Krieger [a], Raul D. Santos [b], Alexandre C. Pereira [a]

[a] Laboratory of Genetics and Molecular Cardiology, Heart Institute (InCor), University of São Paulo Medical School Hospital, São Paulo, Brazil
[b] Lipid Clinic, Heart Institute (InCor), University of São Paulo Medical School Hospital, São Paulo, Brazil

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ABSTRACT

Background and aims: This study reports the first year follow-up of individuals enrolled in Brazil's genetic cascade screening program for Familial Hypercholesterolemia (FH), Hipercol Brasil. Predictors for the occurrence of cardiovascular (CV) events in individuals screened for FH were studied. *Methods*: This is an open prospective cohort of individuals who were included in a cascade genetic screening program for FH. The first prospective follow-up was carried out one year after patients received their genetic test result. Individuals included in this study were index cases (probands) and relatives with identified (M +) or not genetic mutations (M −). Logistic regression analysis was performed to determine predictive variables for the occurrence of CV events censored at one-year of follow-up.
Results: A total of 818 subjects were included, 47 first CV events were ascertained, with 14 (29.7%) being fatal. For index cases, the only factor independently associated with increased risk of CV events was the presence of corneal arcus (OR: 9.39; 95% CI: 2.46–35.82). There was an inverse association of CV events with higher HDL-cholesterol levels (OR: 0.95; 95% CI: 0.90–0.99). For M+ relatives, risk factors associated with increased CV events risk were diabetes mellitus (OR: 7.97; 95% CI: 2.07–30.66) and tobacco consumption (OR: 3.70; 95% CI: 1.09–12.50).
Conclusions: A high one-year incidence of CV events was found in this cascade-screening cohort. Predictors of events differed between index cases and relatives and can be useful for the development of preventive efforts in this highly susceptible group of individuals.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disease clinically characterized by elevated levels of serum low-density lipoprotein-cholesterol (LDL-C) and the occurrence of early cardiovascular disease (CVD) [1–5]. The worldwide prevalence varies from 1:200 to 1:500 in the heterozygous form. The homozygote form is rare and its prevalence is around 1:300,000–1,000,000. In Brazil, it is estimated that there are 402,000 to 670,000 cases of FH and less than 1% are diagnosed and treated appropriately [6–8].

HipercolBrasil program [7] is a nation-wide initiative to provide molecular FH screening for in-risk probands and first-degree relatives. Initially, the Index Case (IC) is clinically identified (LDL-C $\geq$ 210 mg/dL without lipid-lowering drugs) and molecularly tested for a mutation in one of the three known genes that cause heterozygous FH (*LDLR*, *PCSK9* and *APOB*). Once a mutation is detected in an IC, all first-degree relatives (regardless of their cholesterol levels) are invited to participate in the screening program. First-degree relatives have a 50% chance of having the disease [8,9].

FH patients are at high risk for early cardiovascular disease (CVD), since they are exposed to elevated LDL-C levels since birth [10,11]. The risk of cardiovascular (CV) events in these patients may be increased by 20 times if FH is not diagnosed and treated properly [11]. Other factors may increase the risk of CV events in these individuals, such as smoking, hypertension, diabetes, high body mass index (BMI), family history of premature CVD and low levels of HDL cholesterol (HDL-C) [12–16]. However, most studies evaluating the impact of risk factors in FH patients included only probands and

* Corresponding author. Av. Dr. Enéas de Carvalho Aguiar, 44 – Cerqueira Cesar, São Paulo, SP, 05403-900, Brazil.
E-mail address: pam_r_s@usp.br (P.R.S. Silva).

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were derived from retrospective or cross sectional evaluations, thus making the predictors of CV events in relatives still uncertain. In addition, it is tempting to speculate that clinical and demographic determinants of cardiovascular events will vary depending on the final result of the molecular screening program and that this may have important consequences for the care of these individuals. Therefore, the aim of this study was to identify the main CV event predictors in individuals included in a cascade screening cohort for FH, for both probands and relatives.

2. Materials and methods

2.1. Study design

This study evaluated prospectively a cohort of patients who were included in the genetic cascade screening program, HipercolBrasil [7] and was conducted at the Laboratory of Genetics and Molecular Cardiology of the Heart Institute (InCor), University of São Paulo Medical School Hospital, São Paulo, Brazil. The study was approved by the Institutional Ethics Committee (CAPPesq number 3757/12/013).

2.2. Study population and inclusion criteria

The cascade screening program for FH was previously reported by Jannes et al. [7] Index Cases (IC) and relatives summoned by HipercolBrasil program were oriented by trained professionals about the importance of familial genetic screening and written informed consent was obtained from all IC and relatives. For underage individuals (<18 years old), written informed consent was obtained from their legal responsible. The genetic test results were delivered privately in the presence of patients only. In that occasion, patients were instructed about the genetics of FH and the importance of mutation detection. Along with the report, participants received informative folders about FH, cardiovascular disease and the importance of cholesterol control. All patients who agreed to enter the program were registered in the Lipid Clinic of the Heart Institute (InCor/HC-FMUSP), which is the reference tertiary center for treatment and follow-up.

Individuals older than 15 years which were participating in the cascade-screening program were included in the follow-up study once they received the genetic screening report (T0). Study subjects were: IC with suggestive clinical and presenting a definitive genetic diagnosis of FH (M+); IC with suggestive clinical diagnosis but no identified mutations (M−); and relatives with and without identified causal mutations (rM+ and rM−, respectively). Although it is not expected that rM-present a higher risk for CV events when compared to M+ or rM+, these were maintained in the follow-up study so we could assess whether they indeed present no higher risk for CV events, as well to serve as a family-adjusted control group.

2.3. One-year follow-up

To collect data from individuals included in the study, a standardized questionnaire was applied by phone by a trained professional one year after the patient received the result of the genetic test. The follow-up questionnaire ascertained whether the patient presented or not a cardiovascular event during the follow-up. In addition, the questionnaire inquired about previous CVD; presence of risk factors for atherosclerosis; history of early CVD in first-degree relatives (e.g. male <55 and female <60 years-old); current biochemical exams; follow-up with specialists; which medication the patient was using and if there were changes in prescription; adherence to treatment; onset of additional risk factors for cardiovascular events (hypertension, diabetes, smoking); physical activity, and patient's general health. Incomplete treatment adherence was defined as patients failing to take their medication at least 5 times a month.

First cardiovascular events during follow-up were defined as: acute myocardial infarction, unstable angina with hospitalization, coronary angioplasty, coronary artery bypass surgery, ischemic stroke, ischemic heart disease, or congestive heart failure. Cardiovascular events, plasma lipids, presence of CVD risk factors, and use of lipid-lowering drugs were adjudicated from patients' medical records.

2.4. Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 13.0). Initially, a descriptive analysis of the variables was carried out. For continuous variables the mean and standard deviation were calculated. Categorical variables were calculated as frequencies. The differences between frequencies were compared using the chi-square test. The differences between means were compared with Student t or Analysis of variance (ANOVA) tests if necessary. Significance was considered at a p value < 0.05. The logistic regression analysis was performed to determine predictive variables for the occurrence of CV events. The magnitude of the association was estimated using the odds ratio (OR) with 95% confidence intervals (95% CI).

3. Results

3.1. Clinical and laboratory parameters

A total of 818 subjects were included in the study. Tables 1 and 2 show clinical and laboratory characteristics of the subjects in the first year of follow-up, respectively. Of all ICs (n = 299) included in the analysis, 167 (55.8%) were M+ while 132 were M−. Of interest, after one year of follow-up, although 11% of M- IC had their dose of lipid-lowering agents increased, overall this group presented a trend for decrease in the prevalence of lipid-lowering treatment (LLT). For M+, in 18.5% the prescribed doses were increased, without a significant change in the overall prevalence of LLT.

Regarding the lipid profile, Table 2 shows that both M+ and M- IC presented a decrease in total and LDL-C, and an increase in HDL-C levels after one year ($p < 0.05$).

The numbers of relatives included in the analysis were 348 rM+ (67%) and 171 rM−. Table 1 shows that rM + had an increase in the prevalence of diabetes diagnosis, in the use of lipid-lowering drugs and a decrease in tobacco consumption ($p < 0.05$) after one year. Among rM + individuals that were under LLT during the follow-up, 29.8% presented changes in the drug dosage (21.2% with dose increase). However, of all patients under LLT 25.1% reported incomplete adherence to treatment. Table 2 shows that there was no significant alteration in lipid profile of relatives after one year.

3.2. Cardiovascular events during follow-up

During follow-up a total of 47 first new CV events occurred, being 33 (70%) nonfatal: 21.2% myocardial infarction, 15.5% angina, 12.1% coronary artery bypass surgery, 24.2% coronary angioplasty, 12.1% congestive heart failure, 3% ischemic stroke, and 10% ischemic heart disease. Fourteen events (30%) were fatal: 71.4% myocardial infarction, 21.4% congestive heart failure, and 7.1% ischemic stroke. Of all CV events (fatal or non-fatal) in the group of mutation positive individuals (IC and relatives) 24.3% refer to coronary angioplasty and 10.8% to coronary artery bypass surgery.

A total of 37 (7.2%) and 10 (3.3%) events occurred respectively in