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Health related quality of life in individuals at high risk for familial hypercholesterolemia undergoing genetic cascade screening in Brazil

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ABSTRACT

Background and aims: Familial hypercholesterolemia (FH) is a genetic disorder associated with high risk of early major cardiovascular events (MACE) that can impact the health related quality of life (HRQoL), however, this association is unclear. This study evaluated HRQoL in index cases (IC) and first-degree relatives (FDR) of individuals at high risk of FH undergoing genetic cascade screening.
Methods: Data collection was performed before awareness of molecular diagnosis results. Individuals were divided into four groups according to the molecular diagnosis: IC with (IC+) and without (IC-) identified mutations (n = 93 and n = 175, respectively), and affected (FDR+, n = 231) and non-affected (FDR-, n = 159) FDR of IC+. HRQoL measurements, mental (MCS) and physical component (PCS) scores were carried out with SF-12 questionnaire. Associations were tested by generalized linear models.
Results: The mean age was 49 ± 15 years, 42.2% were men, MACE had occurred in 30.7%. Overall, both PCS and MCS did not differ between FH and non-FH individuals, however, IC trended to have lower PCS independent of FH presence (p=0.003). Lower PCS were associated with female sex (p=0.018), lower education (p<0.001), professional inactivity (p=0.028), previous MACE occurrence (p<0.001), hypertension (p=0.016), depression (p<0.001) and obesity (p<0.001). Lower MCS were associated with female sex (p=0.009), previous MACE occurrence (p=0.034), depression (p<0.001) and smoking (p=0.009). Neither the presence of FH causing mutations nor pharmacological lipid lowering treatment was associated with HRQoL.
Conclusions: HRQoL is not reduced in both IC and FDR FH individuals in comparison with their non-affected counterparts. Previous MACE and co-morbidities are associated with reduced HRQoL.

1. Introduction

Familial hypercholesterolemia (FH) is a life-long genetic health condition characterized by elevated low-density lipoprotein-cholesterol (LDL-C) concentrations and is associated with an elevated risk of early atherosclerotic cardiovascular disease (ASCVD) and death. There is consensus that if diagnosed early FH can be successfully managed by use of statins and lifestyle change, lessening related morbidity and mortality [1]. FH is usually detected among individuals with premature coronary heart disease in tertiary care centers, and genetic testing increases efficacy of disease screening due to the autosomal dominant nature of its causing molecular defects [2]. The detection of an index case (IC) facilitates cascade screening of first degree relatives (FDR) and other family members in sequence [3].

Despite strategies for detection, treatment, and management of FH, barriers such as low awareness of the disease and its risks among the general population as well as problems related to lipid lowering treatment adherence, misconceptions about the illness and the side effects of medication, especially statins, or affordability are particularly important gaps, which contribute to heath disparities maintenance [1,4,5].

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In a wide comprehensive conceptual model of prevention and health promotion, psychosocial factors assessment helps identify possible barriers to diagnosis, and adequate adherence to a healthy lifestyle and pharmacological treatment [5]. It is known that psychosocial factors are risk modifiers that add complexity to cardiovascular risk prevention efforts [6].

One important issue for the management of FH individuals is how this disorder could affect health related quality of life (HRQoL). The influence of disease related aspects like the presence of a molecular defect, previous ASCVD manifestations, pharmacological treatment as well as psychosocial aspects on HRQoL of FH individuals is uncertain, especially due to widespread underdiagnosis of the disease [4,7–9]. Genetic cascade screening opens up the possibility of comparing HRQoL in confirmed FH IC as well as in their affected and non-affected FDR. Previous studies from European countries suggest that HRQoL is not reduced in FH patients [7,9–11]. However, due to sociocultural, educational, and economic differences, it is unclear if these findings apply to Brazil, a country with high social and educational inequalities and where FH is severely underdiagnosed.

Identifying variation in HRQoL in genetically-confirmed FH ICs, relative to their non-confirmed counterparts, will provide important information relevant to the in-clinic management of FH patients, and the development of interventions to minimize negative psychological effects of the disease. Thus, the objective of this study was to evaluate self-estimated HRQoL and its associated factors in Brazilian individuals participating in a FH genetic cascade screening program.

2. Materials and methods

2.1. Study population

This is a cross-sectional pre-specified analysis of prospectively collected data from individuals participating in the Hipercol Brasil FH genetic cascade-screening program performed at the Heart Institute (InCor) University of Sao Paulo Medical School Hospital in Sao Paulo, Brazil [12]. This study was approved by the local ethics committee, it follows the declaration of Helsinki orientations and a written informed consent was obtained from all participants included in the biobank.

The inclusion criteria of the present study were age $\geq$18 years in individuals with a clinical suspicion of FH (phenotypic FH individual), e.g. presenting or referring a previous LDL-C $\geq$ 5.4 mmol/L (IC) or be an FDR of an IC who had tested positive (IC+) for FH variants invited to participate in the genetic cascade screening program between April 2011 and May 2014.

2.2. Molecular diagnosis

FH causing mutations were determined on the LDL receptor (*LDLR*), apolipoprotein B (*APOB*) and protein convertase subtilisin kexin type 9 (*PCSK9*) genes, as previously described [12]. In addition to gene sequencing, Multiplex Ligation-dependent Probe Amplification (MLPA) was performed to detect copy number variants.

2.3. Data collection

Data were collected at the first session of genetic diagnosis process, during anamnesis interview without any previous knowledge of genetic test results. Participants completed a questionnaire including self-report measures of sociodemographic and psychosocial ASCVD risk modifiers including age, sex, educational level (>12 and $\leq$ 12 years of study), professional status (professionally active or inactive); previous major cardiovascular event (MACE) status (angina pectoris, myocardial infarction, heart failure, arrhythmias and myocardium revascularization both surgical or percutaneous); risk factors for ASCVD (hypertension, type 2 diabetes, obesity and smoking), awareness of FH aspects (hyperlipidemia diagnosis, clinical suspicion of FH, family history of early ASCVD, family history of hypercholesterolemia), use of pharmacological lipid lowering therapy; depression diagnosis, and HRQoL status.

To participate in the current study, it was required that individuals filled in the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12) questionnaire at the initial screening visit. This questionnaire, previously validated in Brazil [13,14], was used to evaluate HRQoL. HRQoL was assessed using the summary scores, the Physical Summary Component (PSC) and Mental Summary Component (MSC), representing physical and mental summary measures, respectively. For estimation of worst and best quality of life, values below and above 50 ($\pm$10) of PSC and MSC for the studied population were chosen as previously done for FH individuals [7].

2.4. Statistical analysis

Study participants were divided into four groups according to results of the genetic tests: IC and their FDR with or without a confirmed FH-causing mutation respectively IC+, FDR+, IC- and FDR-. Analysis of variance (ANOVA) was used to compare HRQOL levels in the IC and FDR groups followed by Dunn's multiple comparisons test. Generalised linear models were used to evaluate the association of studied parameters, expressed as β coefficients and their 95% confidence intervals (CI), with HRQoL measures (PCS and MCS scores as continuous dependent variables) in the whole study cohort. Models were adjusted for age (per 10-year intervals), sex, educational level, professional status, previous MACE occurrence, risk factors for ASCVD (hypertension, diabetes, obesity, smoking, type 2 diabetes), depression, lipid lowering pharmacological treatment, awareness of FH aspects, and the presence of an FH causing mutation. Coefficients with positive and negative values represent associations with increased and reduced HRQoL, respectively. All analyses were performed using the SPSS v.17.0 software (Chicago, IL, USA) and *p* values were adjusted for multiple comparison by Bonferroni correction if necessary.

3. Results

Of 1030 individuals undergoing cascade screening, 63.8% (n = 658) had complete data for the analysis and were included in the study. The mean age was 49 $\pm$ 15 years, 42.2% (n = 278) were men, 54.3% (n = 358) had $\leq$12 years of study, 58.4% (n = 384) were professionally active and the mean (SD) LDL-C was 5.09 $\pm$ 2.07 mmol/L. The HRQoL PCS and MCS were 47.4 $\pm$ 9.6 (median 50.0, percentiles 25–75 42.8 and 54.90), and 48.5 $\pm$ 9.2 (median 50.9, percentiles 25–75 44.1 and 55.7), respectively. More than half of the studied participants (51%, n = 204) had been referred or summoned for cascade screening from outside InCor's Lipid outpatient clinic. Overall, LDL receptor and *APOB* mutations were found in 49.2% (n = 324) of the individuals, no mutations in *PCSK9* were found.

MACE had occurred in 30.7% (n = 202) of the population. Lipid lowering pharmacological therapy, family history of hypercholesterolemia, familial history of early ASCVD, hyperlipidemia awareness and clinical suspicion of FH were reported by 70.6% (n = 465), 80.4% (n = 529), 60.9% (n = 401), 81.2% (n = 534), 20.2% (n = 133) of individuals, respectively. The frequencies of referred depression, type 2 diabetes, smoking and hypertension were 13.7% (n = 90), 11.1% (n = 73), 11.5% (n = 76), and 34.4% (n = 227), respectively.