Endocrinol Diabetes Nutr. 2018;65(5):280–286

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

ORIGINAL ARTICLE

Cascade screening program for familial hypercholesterolemia☆

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Received 22 July 2017; accepted 27 December 2017
Available online 15 June 2018

KEYWORDS
Atherosclerosis;
Cardiovascular disease;
Familial hypercholesterolemia;
Genetic testing;
Cascade screening

Abstract
Introduction and objective: Early detection of heterozygous familial hypercholesterolemia (HFH) is needed to prevent premature cardiovascular events. Our aim is to describe the course of an HFH screening detection day in the Northern Cadiz Health Area in Spain and to analyze the data recorded.
Subjects and methods: Descriptive study of an FH cascade screening program. Index cases (ICs) and their 1st and 2nd grade relatives were appointed during a weekend by the FH Foundation. Venous blood samples were taken from the subjects for genetic, blood, and chemistry tests; specialized medical consultation and physical examination were performed.
Results: The study sample consisted of 132 subjects: 21 ICs and 111 relatives (16 under 18 years old), with a mean age of 11.4 years (SD 4.57). Mean age of subjects over 18 years was 45.2 years. A gene mutation was found in 90 relatives. Mean age at diagnosis was 25 years (SD 17.7) for relatives and for 36.4 years (SD 17.2; $p = .01$) for ICs. Smoking rate was higher in relatives than in ICs (26.3% vs 4.8%; $p = .02$) and corneal arcus was more common in ICs as compared to relatives (47.6% vs 12.6%; $p < .001$). Prior myocardial infarction was recorded in 14.3% of ICs and 4.2% of relatives respectively ($p = .07$). Maximum lipid lowering treatment was being administered to 43.1%.
Conclusions: The screening detection approach identified the estimated 4% population with HFH in the area, and allows for diagnosing HFH 11.4 years earlier.

☆ Please cite this article as: Rubio-Marín P, Michán-Doña A, Maraver-Delgado J, Arroyo-Olivares R, Barrado Varea R, Pérez de Isla L, et al. Programa de cribado en cascada para la detección de la hipercolesterolemia familiar. Endocrinol Diabetes Nutr. 2018;65:280–286.

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https://doi.org/10.1016/j.endien.2018.05.003

PALABRAS CLAVE
Aterosclerosis;
Enfermedad cardiovascular;
Hipercolesterolemia familiar;
Detección genética;
Cribado en cascada

Programa de cribado en cascada para la detección de la hipercolesterolemia familiar

Resumen
Antecedentes y objetivo: La detección precoz de la hipercolesterolemia familiar heterocigota (HFH) es necesaria para prevenir eventos cardiovasculares prematuros. Nuestro objetivo es describir el desarrollo de una jornada de detección de HF (JHF) en el Área de Gestión Sanitaria Norte de Cádiz (AGSNC) para su cribado en España, así como analizar los datos obtenidos.
Pacientes y métodos: Estudio transversal de una JHF en cascada a la que acudieron los casos índices (CI) diagnosticados genéticamente y sus familiares de primer y segundo grado subsidiarios de presentar HFH. Se analizaron variables clínicas, sociodemográficas y se recogieron muestras biológicas para estudio genético.
Resultados: Se estudiaron 132 sujetos: 21 CI y 111 familiares; 16 eran menores de 18 años, con una edad media de 11,4 años (DE: 4,57). De los mayores de 18 años, el 56% (n = 65) fueron mujeres, con una edad media de 45,2 años (DE: 15,9). Noventa familiares eran portadores de una mutación. La edad media de diagnóstico de los familiares fue de 25 años (DE: 17,7), y la de los CI, de 36,4 años (DE: 17,2); p = 0,01. El tabaquismo activo fue mayor en los familiares que en los CI (26,3% vs 4,8%; p = 0,02) y la presencia de arco corneal en menores de 45 años era más frecuente en los CI (47,6% vs 12,6%; p < 0,001). El 14,3% de CI habían presentado un infarto de miocardio vs el 4,2% de los familiares; p = 0,07. El 43,1% estaban con máximo tratamiento hipolipemiante oral.
Conclusiones: La estrategia de detección en cribado identificó al 4% de la población estimada con HF del AGSNC. Esta búsqueda activa de HF en los familiares anticipa su diagnóstico en 11,4 años.

Introduction

Heterozygous familial hypercholesterolemia (HFH) is the most common genetically based cause of early coronary disease, and up to 10% of all subjects with premature coronary events have FH.[1,2] In Spain, approximately 15% of the HFH population has suffered an atherosclerotic cardiovascular event.[3,4] Heterozygous familial hypercholesterolemia is therefore a public health problem, and its diagnosis and treatment are mandatory. The disease is characterized by an autosomal dominant hereditary pattern and presents in approximately 50% of the offspring of the affected individual.[5,6] The prevalence of HFH has been seen to increase with the progressive introduction of detection programs, from 1/500 to 1/200 individuals in the most recent studies.[7] By contrast, homozygous familial hypercholesterolemia has a much lower prevalence of approximately 1/450,000 individuals.[8] The presence of atherosclerotic cardiovascular disease in HFH can be prevented by the existing lipid-lowering treatment options: statins, ezetimibe[9–11] and/or PCSK9 inhibitors that effectively reduce LDL-cholesterol (LDLc) levels, contributing to the achievement of the LDLc objectives[9–15] and to the reduction of cardiovascular events in these subjects. A precise tool is also available that quantitatively predicts the risk of a new cardiovascular event in this population,[16] though there is still an unmet need to establish an early diagnosis of the disease. Different strategies have been adopted in this regard, such as the approach used in the Netherlands[17] or, in the absence of a similar plan in our country, a weekend screening program such as that conducted by the Familial Hypercholesterolemia Foundation (FHF),[18,19] which contributes to diagnosis and treatment in order to prevent the development of premature cardiovascular disease (CVD).[20] In recent years, economic studies have demonstrated the cost-effectiveness of implementing cascade genetic screening initiatives.[21–23] However, family screening is usually performed in families with an established history of CVD and not on a general population basis for familial hypercholesterolemia. A screening program in our health system is therefore needed.

The purpose of this study was to describe the implementation of a familial cascade detection day or session for the population screening of familial hypercholesterolemia (FHS) in a healthcare area in Cádiz (Spain), and to analyze the clinical and laboratory test data for inclusion in the Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART).

Material and methods

Families with HFH from the *Área de Gestión Sanitaria Norte de Cádiz* (AGSNC), comprising over 450,000 users, were studied. The FHS constitutes a descriptive, cross-sectional study within the previously described SAFEHEART study,[19] developed at Hospital de Jerez de la Frontera by the UGC of Internal Medicine and the FHF. Initially, 32 subjects with a score of 6 or more points were identified according to the clinical criteria of the Dutch Lipid Clinic Network (DLCN) as probable index cases (ICs; subjects most likely to have HFH). These individuals subsequently underwent a genetic study, which confirmed the diagnosis of HFH in 22 of them (68.7%).