DOI: http://dx.doi.org/10.22122/arya.v15i2.1899 Published by Vesnu Publications

CASCADE screening and registry of familial hypercholesterolemia in Iran: Rationale and design

Golnaz Vaseghi[1], Sina Arabi[2], Shaghayegh Haghjooy-Javanmard[3], Mohammadreza Sabri[4], Masoumeh Sadeghi[5], Alireza Khosravi[6], Sonia Zarfeshani[7], Nizal Sarrafzadegan[8]

Original Article

Abstract

BACKGROUND: Familial hypercholesterolemia (FH) is one of the most common genetic disorders, which leads to premature coronary artery disease (CAD). It has been suggested that heterozygous FH affects around 1:250 to 1:500 in the general population or even more than this, and homozygous FH affects 1:1000000 of the population. If patients with FH are not diagnosed and treated early in life, many of them will develop premature CAD event. As most of the patients with FH are undiagnosed, it is recommended that the general population be screened for high risks of the events since early treatments can reduce the risk of premature CADs. The clinical diagnostic criteria for FH consist of increased plasma low-density lipoprotein cholesterol (LDL-C), clinical features and family history of CAD. However, deoxyribonucleic acid (DNA)-based detection of FH mutation has high diagnostic values. As there was no screening for FH in Iran up until now, we have started screening and registering patients with FH using the CASCADE method.

METHODS: We detected FH subjects in the general population by screening laboratories according to their high LDL-C levels (more than 190 mg/dl or 150 mg/dl if receiving treatments), while our second approach was hospital-based in which one screens hospitalized patients with premature CAD events.

RESULTS: We intended to screen families of indexed patients to provide standard care and therapy in order to optimize their LDL-C.

CONCLUSION: This article provides detailed information on the rationale and design of this screening and registry in Iran.

Keywords: Screening, Registries, Familial Hypercholesterolemia, Iran

Date of submission: 23 Oct. 2018, ***Date of acceptance:*** 30 Jan. 2019

Introduction

Familial hypercholesterolemia (FH), an autosomal dominant disorder, is a common genetic condition affecting low-density lipoprotein cholesterol (LDL-C) metabolism with mutations in LDL receptor *(LDL-R)* gene, apolipoprotein B (APOB), a gene encoding the protein constituent of LDL-C, or proprotein convertase subtilsin-kexin type 9 (PCSK9*)*

How to cite this article: Vaseghi G, Arabi S, Haghjooy-Javanmard S, Sabri M, Sadeghi M, Khosravi A, et al. **CASCADE screening and registry of familial hypercholesterolemia in Iran: Rationale and design.** ARYA Atheroscler 2019; 15(2): 53-8.

1- Assistant Professor, Applied Physiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Student of Medicine, Applied Physiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Professor, Applied Physiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Professor, Pediatric Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Professor, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
6- Professor, Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
7- Interventional Cardiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
8- Professor, Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Nizal Sarrafzadegan, Email: nsarrafzadegan@gmail.com

a gene encoding a protease that degrades LDL-C receptors. It is estimated that heterozygous FH exists 1 out of 500 to 1 out of 250 and in some areas could be up to 1 out of 100 in the general population which is more common than cystic fibrosis (CF), diabetes mellitus (DM), or neonatal hypothyroidism. These figures are even much higher in certain populations such as the French Canadians or Christian Lebanese.[1,2] FH is characterized by LDL-C level above 190 mg/dl, and in some patients it is characterized with the presence of xanthelasma palpebrarum (XP), corneal arcus, as well as the presence of xanthoma on the tendons of hands, elbows, knees, feet, and particularly the Achilles tendon.[3]

Because of a lifelong burden of high LDL-C levels, individuals with FH have a > 20-fold increased risk of premature coronary artery disease (CAD) compared with the general population.[4] Untreated men have a 50% risk of a coronary event by the age of 50, while untreated women have a 30% risk by the age of 60.[5] If the treatment is initiated in young adulthood, patients with FH will have nearly the same risk of CAD compared to their healthy counterparts. They demand lifelong pharmacotherapy with different lipid-lowering medications, dietary management, and modification of other risk factors to prevent cardiac diseases. Unfortunately, physicians are either unaware of the importance of early FH diagnosis or its prevalence or incidence in different countries. FH is a significant global public health concern; patients are often asymptomatic. As a result, an appropriate method to improve detection, management, and treatment of FH in order to decrease premature CAD events and its related death tolls are required among different populations. Previous studies showed that the prevalence of definite FH in premature CAD was about 5-10 percent based on the clinical phenotype.[6,7] However, the true prevalence would be much higher.

Due to the fact that the premature CAD events and its death tolls can be significantly decreased by early diagnosis and proper treatments and also based on our estimates that FH is underdiagnosed and undertreated in Iran,[8] we decided to perform FH screening and registry in the general population and in premature cardiac patients using the CASCADE screening method.[9]

The CASCADE screening method provides a cost-effective way of identifying new cases of FH. Using this method, a person diagnosed with FH and referred to as the indexed case, becomes the starting point for treatment among his or her family members among which a systemic screening of the close relatives is implemented.

We believe that this FH registry will be a powerful tool for monitoring the patients and their families. Using this method provides the health decision makers with pivotal information that can be used in promoting our clinical practice. In addition, we will study other CAD risk factors, identify family members with existing or new FH diagnosis, and develop a bio-bank of deoxyribonucleic acid (DNA) and other biomaterials of patients with FH and their close relatives for future genetic and epigenetic studies. We intend to screen the suspected FH cases by using two approaches. The first approach deals with detecting our cases in the general population by screening their LDL-C levels whereas the second approach was a hospital-based one aimed to screen patients who have been hospitalized due to premature CAD events. This article provides detailed and precise information on the rationale and design of the above-mentioned approaches in Iran.

Materials and Methods

The enrollment framework in these approaches was based on first investigating laboratories for contacting patients with high LDL-C to enroll them in our study (National Clinical Trial No.2865694). All individuals aged above 2 years, irrespective of their sex with LDL-C of more than 150 mg/dl (LDL-C > 190 mg/dl or LDL-C > 150 mg/dl but under pharmacological treatments were considered eligible) were contacted by phone to come to our clinic for further evaluation. We used the Dutch Lipid Clinic Network Score (DLCNS) which was based on the clinical symptoms of FH and family history[9] (Table 1).

Our patient screening was based on young patients with CAD (men less than 55 years old and women less than 60 years) who were hospitalized for percutaneous coronary interventions (PCI) in hospitals with specialized cardiology facilities (National Clinical Trial No.02870660) in Isfahan, Iran.

Our key exclusion criteria were those suffering from genetically hyperlipidemia (secondary hyperlipidemia), patients with chest pain and CADs along with concomitant serious diseases, and those who were previously screened.

All subjects were referred to our FH clinic to be registered. Then they were asked to complete a questionnaire which included demographic characteristics such as physical examination looking

for tendon xanthomas and corneal arcus, the history of CAD and other diseases in the patients or their families, and the medications being used, especially anti-lipid drugs and other medications. In order to be able to follow them for a year, their addresses and phone numbers were collected.

We performed our clinical examination with emphasis on the presence of tendon xanthoma, xanthelasma, or corneal arcus. Finally, the total Dutch criteria score indicates the probability of having or not having FH. Accordingly, people are divided into 4 categories: those whose scores are below 3 are very unlikely to have FH and those whose scores are above 8 are definitely affected by FH. People with scores between 3 and 8 have moderate and high risks of having FH; therefore, those whose scores are more than 8 definitely suffer FH, those whose scores are between 6–8 probably suffer from FH, and those whose scores are between 3–5 possibly suffer from FH[10] (Table1).

All participants underwent a complete blood test consisting of high-density lipoprotein cholesterol (HDL-C), LDL-C, triglyceride (TG), fasting blood sugar (FBS), and other blood indices such as red blood cells (RBC), white blood cells (WBC), platelet count, red cell distribution width (RDW), platelet distribution width (PDW), hematocrit (HCT), and hemoglobin (Hb). The patients' DNA was extracted and frozen for further genetic evaluation.

Management and CASCADE testing: This method has also been used in other countries that have performed FH registry including the Netherlands and Canada. The CASCADE FH Registry is a national, multicenter initiative that tracks FH therapy, family screening, clinical outcomes, and patient-reported outcomes longitudinally.[11] The CASCADE FH Registry represents collaboration among the FH registry team, lipid specialists, cardiologists, primary care providers, and subjects with FH.[12] Our FH registry team implemented a recruitment design to maximize the participation of confirmed and suspected patients with FH. Figure 1 shows the algorithm of our study design.

Results

Upon the approval of probable or definite FH diagnosis, patients would be managed by a specialist if necessary. Patients' lipid levels and cholesterol-lowering medication would be monitored every 3 months along with other lifestyle factors. Our team was responsible for the CASCADE testing of FH relatives. It was expected that up to 50% of first relatives would be diagnosed with FH; however, it was acknowledged that not all relatives would be followed up as they might decline the follow-up.[12]

Data were stored in a password-protected database on a secure server. Only specified research personnel were permitted to have access to the data.

Analyses were conducted using Stata software (version 13, Stata Corporation, College Station, TX, USA). Descriptive statistics were used to outline the number of patients at each point of the study (screened, at risk, followed up, and clinically diagnosed with FH).

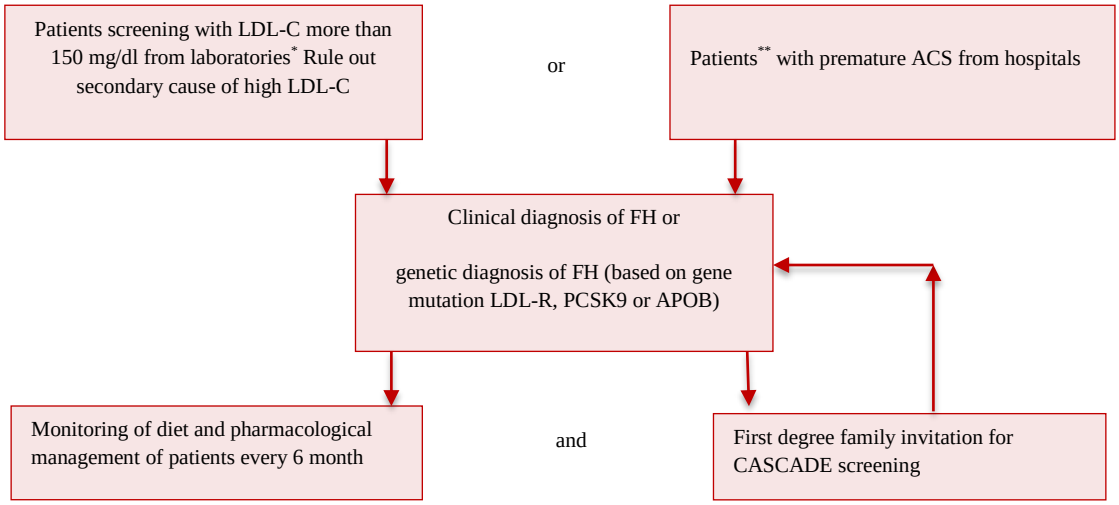

Figure 1. Schematic representation of the patient screening process for registry enrollment
* Rule out secondary cause of high LDL-C
** Age > 65 or > 55 for women and men, respectively
LDL-C: Low-density lipoprotein cholesterol; ACS: Acute coronary syndrome; FH: Familial hypercholesterolemia; LDL-R: Low-density lipoprotein receptor; PCSK9: Proprotein convertase subtilsin-kexin type 9;APOB: Apolipoprotein B

Table 1. Dutch lipid clinic network score (DLCNS) for diagnosis of familial hypercholesterolemia (FH)

Criteria	Score
Family history	
First-degree relative with known premature coronary and vascular disease	1
OR	
First-degree relative with known LDL-C level above the 95th percentile	2
Clinical history	
Patient with premature CAD	2
Patient with premature cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Corneal arcus prior to 45 years of age	4
LDL-C levels (mg/dl, mmol/l)	
≥ 330, ≥ 8.5	8
250–329, 6.5–8.4	5
190–249, 5.0–6.4	3
155–189, 4.0–4.9	1
DNA analysis	
Functional mutation in the LDL-R, APOB, or PCSK9 genes	8
Diagnosis (based on the total number of points obtained)	
Definite FH	> 8
Probable FH	6-8
Possible FH	3-5
Unlikely FH	< 3

LDL-C: Low-density lipoprotein cholesterol; CAD: Coronary artery disease; DNA: Deoxyribonucleic acid; LDL-R: Low-density lipoprotein receptor; APOB: Apolipoprotein B; PCSK9: Proprotein convertase subtilsin-kexin type 9; FH: Familial hypercholesterolemia

At 12 months, the number of new index cases and the number of new family cases that have been detected would be reported. Changes in LDL-C level would be examined using a multilevel mixed-effects modelling. LDL-C level at 12 months would be the dependent variable. Random effects included: authorized medical staff (cluster effects) and time (repeated observations on the same individual). Analysis would also be adjusted for sex and age.

Discussion

Isfahan FH registry as the first FH registry in Iran will provide important evidence on the detection, prevalence, and management of patients with FH. It is well-known that registries are helpful in rapid and efficient collection of data that can be useful for further research, clinical practice, and health policy making. Many researchers prefer using registries' data as they allow the analysis of a disease in real-life conditions. Data obtained from registries provide a perspective of a problem in the community and allow for comparison of the results with large reference populations. This can stimulate improvements in quality and consistency of the practice.[13]

FH registries and screening methods are either general population or selective screening which is based on specific criteria. The selective screening methods can be classified into different categories such as: 1) collective lipid and genetic screening, 2) genetic CASCADE screening, 3) lipid CASCADE screening, 4) family CASCADE screening, and 5) based on a family history of dyslipidemia or coronary or CVD risk factors in the screened person.[14,15]

Isfahan FH registry can increase our knowledge on the burden of FH in Iran. Its results will enable comparisons of the attitudes and practices held in different disciplines including cardiology, internal medicine, and endocrinology. However, the calculation of FH prevalence may be difficult. In this study, we used the CASCADE method to detect patients with FH for both of our approaches. Our criterion for recruitment was high LDL-C level which was above 150 mg/dl (190 mg/dl if subjects did not receive treatments). Subjects were recruited from laboratories and invited to visit our FH clinic to undergo genotyping too. It became an integral part of clinical practice for FH, so all patients underwent genetic tests.

The Dutch criteria for the diagnosis of FH are a modification of the Simon-Broome criteria.[9] The principal reason for developing the Dutch criteria is that the Simon-Broome criteria diagnoses FH based

on personal and family history, physical examination, and laboratory findings. To address this shortcoming, the Dutch criteria introduce a point system and take the molecular defect of FH into consideration. Therefore, we studied our FH participants and classified them to different categories. Accordingly, they were defined as definite, probable, or possible.[3,14]

The advantages of our work are using an internationally well-known method, using two approaches at the population and premature CAD patients' levels, face-to-face examination of the participants, looking for examining the presence of tendon xanthomata and corneal arcus in addition to developing a bio bank of future genetic and other studies.

Our limitation is not performing genetic study simultaneously to conform the final Dutch criteria score at this stage.

Conclusion

Isfahan FH registry is the first FH registry in Iran which will generate valuable evidence regarding the diagnosis and management of these patients in this country. This will fill the gap in preventive care and establish the effective treatments of FH. While the implementation has been initiated in Isfahan, the scale-up pilot study at the national level will be started which may improve the quality and consistency of clinical practice and lead to the establishment of a national policy for the diagnosis and treatment of patients with FH. These data would be a source for local and international research.

Acknowledgments

This work was partly supported by the National Institute for Medical Research Development (NIMAD) (research grant: No.943785). Additionally, this work was partly supported by Behestan Darou Company and Spadan Heart Health Foundation. The funding agencies had no role in the design of the study. Moreover, they played no role in collection, analysis, and interpretation of the data.

Conflict of Interests

Authors have no conflict of interests.

References

1. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011; 5(3 Suppl): S1-S8.

2. Yuan G, Wang J, Hegele RA. Heterozygous familial hypercholesterolemia: An underrecognized cause of early cardiovascular disease. CMAJ 2006; 174(8): 1124-9.

3. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: A HuGE prevalence review. Am J Epidemiol 2004; 160(5): 407-20.

4. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ. Familial hypercholesterolemias: Prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011; 5(3 Suppl): S9-17.

5. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients: Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011; 5(3): 133-40.

6. Pilote L, Karp I. GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: From bench to beyond-Premature Acute Coronary SYndrome). Am Heart J 2012; 163(5): 741-6.

7. Faggiano P, Pirillo A, Griffo R, Ambrosetti M, Pedretti R, Scorcu G, et al. Prevalence and management of familial hypercholesterolemia in patients with coronary artery disease: The heredity survey. Int J Cardiol 2018; 252: 193-8.

8. Shirani S, Kelishadi R, Sarrafzadegan N, Khosravi A, Sadri G, Amani A, et al. Awareness, treatment and control of hypertension, dyslipidaemia and diabetes mellitus in an Iranian population: The IHHP study. East Mediterr Health J 2009; 15(6): 1455-63.

9. Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis 2004; 173(1): 55-68.

10. Williams RR, Hunt SC, Schumacher MC, Hegele RA, Leppert MF, Ludwig EH, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol 1993; 72(2): 171-6.

11. O'Brien EC, Roe MT, Fraulo ES, Peterson ED, Ballantyne CM, Genest J, et al. Rationale and design of the familial hypercholesterolemia foundation CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia registry. Am Heart J 2014; 167(3): 342-9.

12. Wierzbicki AS, Humphries SE, Minhas R. Familial

hypercholesterolaemia: Summary of NICE guidance. BMJ 2008; 337: a1095.
13. Hadfield SG, Horara S, Starr BJ, Yazdgerdi S, Marks D, Bhatnagar D, et al. Family tracing to identify patients with familial hypercholesterolaemia: The second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. Ann Clin Biochem 2009; 46(Pt 1): 24-32.
14. Harada-Shiba M, Arai H, Ishigaki Y, Ishibashi S, Okamura T, Ogura M, et al. Guidelines for diagnosis and treatment of familial hypercholesterolemia 2017. J Atheroscler Thromb 2018; 25(8): 751-70.
15. Langslet G, Ose L. Screening methods in the diagnosis and assessment of children and adolescents with familial hypercholesterolemia. Expert Rev Cardiovasc Ther 2013; 11(8): 1061-6.