Atherosclerosis 277 (2018) 278–281

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Familial hypercholesterolemia screening program in Bosnia and Herzegovina and cardiovascular morbidity

Lamija Pojskic*, Belma Pojskic

Department for Internal Diseases and Hemodialysis, Cantonal Hospital Zenica, Bosnia and Herzegovina

ARTICLE INFO

Article history:
Received 31 March 2018
Received in revised form
16 June 2018
Accepted 21 June 2018

Keywords:
Familial hypercholesterolemia
Screening
Cardiovascular disease

ABSTRACT

Background and aims: We aimed to estimate the frequency of cardiovascular diseases in familial hypercholesterolemia (FH) patients in Bosnia and Herzegovina.

Methods: We screened lipid profiles in the hospital system during the period March 2008–November 2016, and included 307 patients with LDL>4.5 mmol/L. FH was diagnosed according to the Dutch Lipid Clinic Network (DLCN) criteria. Followed parameters were: the presence of coronary artery disease (CAD), premature CAD (defined as men<55yrs,women<65yrs), cerebral vascular disease (CVD). Patients were divided into 4 groups according to the DLCN criteria: Group1 - definite FH, Group2 - probable FH, Group 3 - possible FH, Group4 - unlikely FH. Patients with incomplete data and secondary causes of hyperlipidemia were not included. Statistical analysis was done using the SPSS software package Version 19.0.

Results: There were 307 patients. Group1 counted 16 patients; Group2, 56; Group3, 140, and Group4, 95. In Group1, CAD was diagnosed in 7 patients (43.75%); PCAD in 7 (43.75%); CVD in 2 (12.5%). In Group2, CAD was diagnosed in 25 patients (44.6%); PCAD in 23 (41.1%); and CVD in 8 (14.3%). In Group3, CAD was diagnosed in 64 cases (45.7%); PCAD in 29 (20.7%); and CVD in 47 (33.6%). In Group4, CAD was diagnosed in 19 patients (20%); PCAD in 3 (3.2%); and CVD in 73 (76.8%). CAD was significantly more present in Groups 1,2 and 3 compared with Group4. Occurrence of PCAD was statistically significant in patients with definite and probable FH compared with Groups 3 and 4 ($p < 0.05$). There was a significant difference in the appearance of CVD in Group4 compared with Groups 1,2 and 3.

Conclusions: Definitive and possible FH groups were strongly associated with PCAD and CAD, while CVD was significantly higher in the unlikely FH group. Screening program and worldwide information exchange are essential to spread the knowledge about FH prevalence.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder characterized by elevated plasma low-density lipoprotein cholesterol (LDL-C) levels [1,2]. It is a common cause of premature coronary heart disease [1]. The diagnosis of FH is, in most cases, based on the clinical picture and Dutch Lipid Clinic Network (DLCN) criteria. It is recommended to confirm diagnosis with DNA analysis, when available [3]. Once diagnosed, FH can be treated and coronary heart disease can be postponed or even prevented. Estimated prevalence of FH worldwide is 1/500–1/200, but it is vastly underdiagnosed, and even when diagnosed it is undertreated [1]. When an index case is identified by the DLCN criteria or genetic testing, it is recommended to conduct a cascade screening in family [1,3].

Screening program for familial hypercholesterolemia in Bosnia and Herzegovina (B&H) has begun three years ago under almost simultaneous patronage of the European Atherosclerosis Society (EAS) and ScreenPro FH. Estimated prevalence in B&H is 1:500 or 7062 F H patients. National center for ScreenPro FH is the Cantonal Hospital Zenica. Diagnosis is based on DLCN criteria since genetic testing is not available in B&H [4]. Screening program in B&H is facing many challenges. The most prominent issue remains the limited knowledge and lack of awareness of FH, which we are trying to overcome through lectures, media, and by publishing a book about FH [5]. In addition, an important issue is lack of data, especially value of LDL-C and incomplete family history, which

* Corresponding author. Department for Internal diseases and Hemodialysis Cantonal Hospital Zenica, Crkvice 67, 72000 Zenica, Bosnia and Herzegovina.
E-mail address: lamija.pojskic@gmail.com (L. Pojskic).

https://doi.org/10.1016/j.atherosclerosis.2018.06.880
0021-9150/

make clinical diagnosis more difficult. Nowadays data about FH are significant and indicate a more frequent prevalence of FH than we assumed at the beginning of the project.

There are several treatment possibilities for FH patients [6]. Primary target of cholesterol-lowering therapy is elevated LDL-C since recent clinical trials showed that LDL-lowering therapy reduces the risk for coronary heart disease [7]. The goal of treatment is to reduce LDL-C by 50% from baseline levels. First step is lifestyle modification, but it is insufficient as sole treatment to achieve the LDL-C goal. At most, it can reduce LDL-C concentration by 10–15% and the pharmacological treatment is required for most patients [8]. Standard pharmacological treatment for patients with FH is high-intensity statin therapy. Most patients need combination therapy because LDL-C levels remain above those recommended by the guidelines. Combination therapy of statin and ezetimibe is common and successful. Additional drugs such as mipomersen and lomitapide are effective in reducing LDL-C levels, but they have important adverse effects and are currently indicated only for treatment of homozygous FH [6,9]. The most promising emerging treatment is represented by PCSK9 inhibitors (alirocumab or evolocumab) in combination with statins [6]. LDL-C apheresis is a cornerstone in treatment of patients with homozygous FH and more severe heterozygous FH when other lipid-lowering therapies are ineffective [10,11]. The only available pharmacological treatment in B&H is statin therapy (rosuvastatin, atorvastatin, simvastatin), and LDL-C apheresis is not available [5].

In this article, we were interested in the frequency of FH in hospital-treated patients suffering from cardiovascular diseases.

2. Materials and methods

We screened lipid profiles of the hospital information system (Cantonal Hospital Zenica) in the period March 2008–November 2016 and enrolled 307 patients with fasting LDL-C >4.5 mmol/L. FH was diagnosed according to the DLCN criteria [3]. Genetic testing was not available. Fasting levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) were measured, and LDL-C was calculated according to the Friedewald's formula [12]. Followed parameters were: the presence of coronary artery disease (CAD), premature CAD (PCAD), cerebral vascular disease (CVD).

2.1. Study population

This study was retrospective; data were collected from patients with dyslipidemia and CAD, PCAD and CVD. All patients were hospitalized between March 2008 and November 2016, at the Cantonal Hospital Zenica. A criterion for dyslipidemia was LDL >4.5 mmol/L.

CAD was considered to be present if patients had a documented history of myocardial infarction, an abnormal coronary angiogram (stenosis >70% in a major vessel), percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG).

Premature CAD is defined as appearance of CAD in men younger than 55 years and women younger than 65.

Cerebrovascular disease was considered when computer tomography findings were positive.

FH possibility was calculated according to the DLCN criteria [1–3]. Patients were divided into 4 groups according to DLCN criteria: Group1 - definite FH; Group2 - probable FH; Group3 - possible FH; Group4 - unlikely FH. We did not include patients with missing values for required parameters, patients with possible secondary causes of hyperlipidemia such as diabetes mellitus, hypothyroidism, chronic renal failure, nephrotic syndrome, excessive alcohol consumption; patients with high TG, age <18 years.

We investigated the presence and possibility of FH in patients with CAD, PCAD, and CVD.

2.2. Ethics statement

The study protocol was approved by the institutional ethical committee (Ethics committee of Cantonal Hospital Zenica).

2.3. Statistical analysis

Statistical analysis was done using the SPSS software package Version 20.0. The data are presented as number or percentage, and they were tested for normality of distribution. For statistical analysis, $\chi 2$ test, Fischer's Exact test and descriptive statistics were used. p values < 0.05 were considered as statistically significant.

3. Results

Among the 307 patients: in Group1, 16 had definite FH; in Group2, 56 had probable FH; in Group3, 140 had possible FH; and in Group4, 95 had unlikely FH (Table 1).

In Group1, CAD was diagnosed in 7 cases (43.75%); PCAD in 7 (43.75%); and CVD in 2 (12.5%). In Group2, CAD was diagnosed in 25 patients (44.6%); PCAD in 23 (41.1%); and CVD in 8 (14.3%). In Group3, CAD was diagnosed in 64 patients (45.7%); PCAD in 29 (20.7%); and CVD in 47 (33.6%). In Group4, CAD was diagnosed in 19 cases (20%); PCAD in 3 (3.2%); and CVD in 73 (76.8%) (Fig. 1 and Fig. 2).

There was no significant difference in the appearance of CAD between Groups 1 and 2, Groups 1 and 3, Groups 2 and 3. Significantly more patients had CAD in Groups 1, 2 and 3 when each group was compared to Group4 ($p < 0.05$).

Occurrence of PCAD was statistically significant in patients with definite and probable FH (Group 1 and Group 2) when compared with Groups 3 and 4 ($p < 0.05$), and in Group3 when compared with Group4 ($p < 0.05$).

CVD was statistically significantly more represented in Group4 than in Groups 1, 2 and 3. In Group3, there were significantly more patients with CVD than in Group2 ($p < 0.05$).

4. Discussion

This is the first study to report on FH and cardiovascular diseases in Bosnia and Herzegovina. When we began our screening program in 2015, familial hypercholesterolemia as common genetic disorder was largely unknown to both physicians and patients [5]. The beginning of the screening program encountered many difficulties. Beside the lack of knowledge and awareness about FH, one of the most prominent issues was and the lack of data required for clinical diagnosis of FH, mainly lack of LDL value.

In this study, we screened lipid profiles of hospitalized patients at the Cantonal Hospital Zenica during the period March

Table 1
Number of patients with CAD, PCAD, and CVD according to DLCNS.

	FH definitive	FH probable	FH possible	Unlikely FH	Score
CAD	7	25	64	19	115
PCAD	7	23	29	3	62
CVD	2	8	47	73	130
Score	16	56	140	95	307

FH – familial hypercholesterolemia, CAD – coronary artery disease, PCAD – premature coronary artery disease, CVD – cerebrovascular disease, DLCNS – Dutch Lipid Clinical Network Score.