Atherosclerosis 277 (2018) 347–354

Contents lists available at ScienceDirect

Atherosclerosis

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

Latvian registry of familial hypercholesterolemia: The first report of three-year results

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ARTICLE INFO

Article history:
Received 23 March 2018
Received in revised form
17 May 2018
Accepted 7 June 2018

Keywords:
Cholesterol
Familial hypercholesterolemia
Low-density lipoprotein cholesterol goal
Registry

ABSTRACT

Background and aims: Familial hypercholesterolemia (FH) was rarely diagnosed in Latvia before 2015, when the Latvian Registry of FH (LRFH) was established. Here, we report the first experience of the LRFH over three years (2015–2017).
Methods: The LRFH is an ongoing nationwide, dynamic, long-term prospective cohort. The diagnosis of FH was assessed using the Dutch Lipid Clinic Network (*DLCN*) criteria. Cascade screening of first-degree relatives using age- and sex-specific percentiles of low-density lipoprotein cholesterol (LDL-C) was performed in relatives of patients with definite and probable FH.
Results: Among the 416 individuals included in the LRFH, 181 patients were diagnosed with FH (140 index cases and 41 relatives) and 151 with possible FH (not analysed in this report). The mean age was 51.3 ± 14.1 years, 38.1% (n = 69) were men and 35.4% (n = 64) had a history of premature coronary heart disease. Only 54.1% (n = 98) of patients were on any lipid-lowering therapy before inclusion in the LRFH. The maximal statin dose was used by 23.2% (n = 42), and only 4.4% (n = 8) had their LDL-C levels below the goal. The initial mean total and LDL-C levels were 7.7 ± 2.2 and 5.5 ± 2.1 mmol/L, respectively. In a subgroup of patients (n = 49) with follow-up, LDL-C levels were reduced from 6.1 ± 2.1 to 3.6 ± 1.7 mmol/L ($p < 0.001$).
Conclusions: An estimated 2.3% of FH patients in Latvia were diagnosed within three years. The vast majority of FH patients were under-recognized and poorly treated before their inclusion in the LRFH. Specialized care of FH patients within the frames of the registry substantially improved the management of this high-risk group.

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1. Introduction

Familial hypercholesterolemia (FH) is the most common form of primary lipoprotein metabolism disorder that is responsible for the development of premature atherosclerotic cardiovascular disease (ASCVD), with coronary heart disease (CHD) being the most prevalent manifestation [1,2]. This inherited disease is typically caused by genetic mutations that impair uptake of low-density lipoprotein (LDL) particles by the liver, which leads to life-long exposure of the arteries to very high levels of LDL-cholesterol (LDL-C) [3,4]. Consequently, patients with FH have a particularly high risk of developing ASCVD that is often premature (age <55 years in men and <60 years in women) [1,2].

In six large epidemiologic US cohorts, the long-term FH phenotype (defined as LDL-C levels ≥4.9 mmol/L) was associated with an acceleration of CHD risk by 10–20 years in men and 20–30 years in women [5]. Importantly, the highest relative risk was observed in younger ages and as early as 20–29 years. Furthermore, the relative risk of developing CHD was 22.0 in patients with LDL-C ≥4.9 mmol/L who were carriers of the FH mutation, compared to a relative risk of 6.0 in mutation-negative individuals with similarly high LDL-C levels [6].

Early initiation of lipid-lowering therapy lowers the LDL-C levels, providing a longer life expectancy and reducing the risk of CHD in FH [7,8]. The timely recognition and treatment of FH patients are, therefore, crucial to make an early diagnosis and

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https://doi.org/10.1016/j.atherosclerosis.2018.06.011
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effectively prevent the risk of ASCVD with lipid-lowering treatments. Nationwide FH registries play an important role in improving patient management and help measure healthcare delivery, plan financial resources, conduct clinical research and educate professionals, patients, the general population and healthcare providers [9–11].

Before 2015, it was extremely rare for physicians to diagnose FH in Latvia due to the very low professional and public awareness of the disease. The number of diagnosed cases in the country was unknown, and we estimate that percentage of individuals diagnosed with FH was probably approximately 0.2%. The Latvian Registry of Familial Hypercholesterolemia (LRFH) was established in February 2015 as an effort to improve FH diagnostics in Latvian patients and their relatives by screening patients with hypercholesterolemia, consulting and treating these individuals, and increasing awareness among general practitioners and the public of FH. Here, we report the first results of the LRFH, covering the three-year period of 2015–2017.

2. Patients and methods

2.1. Study population

The LRFH is a nationwide dynamic, long-term prospective cohort. All patients were seen at the Latvian Centre of Cardiology, Pauls Stradins Clinical University Hospital. The study was approved by the local medical ethics committee. Written informed consent was obtained in all individuals prior to inclusion in the Registry. Recruitment of FH patients started in February 2015 and is still ongoing. The study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki. All persons were also invited to take part at the Genome Database of Latvian Population, which required additional informed consent [12].

The following referral criteria were used: (i) documented total cholesterol (TC) $\geq$7.0 mmol/L and/or LDL-C >5.0 mmol/L, or (ii) known premature CHD (patient or first-degree relative aged <55 in men or <60 in women; second-degree relative <50 in men or <55 in women), or (iii) tendon xanthomas in patient or first-degree-relative, or (iv) resuscitated premature cardiac death or premature cardiac death in family history, or (v) TC > 6.0 mmol/L and/or LDL-C > 4.0 mmol/L or above the 95 t h percentile in a first degree relative, or (vi) known (probable or definite) FH in a first- or second-degree relative. The referral criteria were based on the recommendations of the 2013 European Atherosclerosis Society (EAS) Consensus Statement with modifications [1]. Only adult patients were included in the registry. Most patients were referred to the LRFH by their family doctors and cardiologists or by specialists such as internists, endocrinologists, cardiac and vascular surgeons or neurologists. Typically, it was recommended that patients contact the coordinator of the LRFH to sign up for a consultation by calling the mobile phone of the registry. Several cases were discovered by physicians at the Pauls Stradins Clinical Hospital and discussed together with the registry representatives. Some patients contacted the registry directly as public awareness of the registry's activities grew.

All patients were interviewed about personal medical history and investigations as well as family history. Physical activity was evaluated in metabolic equivalents of task (METs). Dietary habits were measured according to the PREDIMED score [13]. Routine physical examination was performed and included heart and lung auscultation, measurement of blood pressure (BP), body mass index (BMI) and waist circumference, evaluation for the presence of corneal arcus and tendon xanthomas in four muscle extensor groups: Achilles tendon, finger extensor tendons, patellar and triceps tendons [14].

First-time patients referred for opportunistic screening were evaluated according to the Dutch Lipid Clinic Network (DLCN) criteria, as recommended by the EAS and the European Society of Cardiology (ESC) [1,15]. In cases of definite or probable FH, clinical diagnosis of FH ("clinical FH") was made and cascade screening recommended in the first-degree relatives. The diagnosis of FH was made in the first-degree relatives with an LDL-C level above age- and sex-specific 95th percentile values or if they met criteria for definite or probable FH [16].

It was recommended that all patients test their thyroid-stimulating hormone (TSH), total protein and albumin levels and have a urinalysis to rule out any potential secondary causes of elevated LDL-C; it was also suggested that lipoprotein(a) levels be measured for additional risk evaluation. Information about main variables included in the database are summarized in the data dictionary (Supplementary Table 1). Plasma samples were obtained from peripheral venous puncture and stored at −80° Celsius. Additional blood was obtained during the same venous puncture and sent to the Latvian Biomedical Research and Study Centre for DNA storage, if patients consented to take part in the Latvian Genome Data Base. Recommendations about lifestyle, treatments and lipid goals were made according to the guidelines and scientific consensus documents available at the time [1,15,17–19]. When cascade screening was indicated, patients were offered an opportunity to forward letters to their first-degree relatives. PASS Clinical® Vascular was used to draw family trees.

2.2. Statistical analysis

Continuous variables are shown as the mean arithmetic and standard deviation if normally distributed and as the median and inter-quartile range if the distribution was non-normal. Categorical variables were shown as count and percentage. Normally distributed continuous variables were compared with Student's *t*-test for independent samples for two groups. Non-normally distributed continuous variables were compared with the Mann-Witney *U* test. Categorical variables were compared using the chi-square test or Fisher's test as appropriate. Repeated data measurements were compared with a paired *t*-test for normally distributed variables, the Wilcoxon test for non-normally distributed variables, and the McNemar test for binary variables. All results were analysed using IBM SPSS 22.0 software. The results with *p* values below 0.05 were considered statistically significant.

3. Results

3.1. General characteristics of the study population

Data on 416 individuals were included in the database of the LRFH between February 2015 and December 2017. The dynamics of patient inclusion for three years are depicted in Fig. 1. The majority (n = 348, 83.7%) were index cases referred for opportunistic screening, and FH (definite or probable) was diagnosed in 140 (40.2%) of these patients. The diagnostic categories according to the Dutch Lipid Clinic Network criteria in index cases (n = 348) were the following: 63 definite FH (18.1%), 77 probable FH (22.1%), 151 possible FH (43.4%) and 57 unlikely FH (16.4%). Cascade screening was performed in 68 first-degree relatives, and FH was diagnosed in 41 (60.3%) cases. Thus, in total, 181 patients between 18 and 86 years were diagnosed with FH, and their data are presented further. The general characteristics of FH patients are summarized in Table 1.

3.2. Non-lipid risk factors

Most patients had never smoked, while 18.2% were active

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