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Establishing a national screening programme for familial hypercholesterolaemia in Lithuania

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ABSTRACT

Background and aims: Familial hypercholesterolaemia (FH) is a widely underdiagnosed genetic disorder characterized by severely elevated levels of serum cholesterol and associated with premature mortality. Screening programmes and registries have been established worldwide to find and monitor patients with FH. The aim of this paper was to describe the approaches currently applied to identify patients with possible FH in Lithuania.

Methods: An electronic extraction tool was applied to the medical records of 92,373 subjects evaluated in primary care settings from 2009 to 2016, 1714 secondary prevention patients with early onset (<50 years) coronary heart disease (CHD) treated in tertiary care hospital from 2005 to 2016 and high-risk subjects in specialized cardiovascular prevention units. The electronic databases were screened for likely FH phenotype, which was described simply as LDL-C $\geq$6.5 mmol/l.

Results: Likely FH phenotype was observed in 1385 (1.5%) middle-aged Lithuanians, 290 (16.9%) people with premature CHD and 330 adults from high-risk subjects referred to specialized cardiovascular prevention units. A total of 2005 patients with likely phenotypic FH were included in the Lithuanian FH screening programme, covering about 15% of estimated FH cases in Lithuania.

Conclusions: Screening for extremely elevated LDL-C levels in primary prevention database and additional enrolment of patients with premature CVD as well as high-risk subjects may be a valid way to set up a national FH screening programme. It is crucially important to identify and initiate the treatment of FH patients as early as possible to reduce high cardiovascular mortality in these patients.

1. Introduction

Familial hypercholesterolaemia (FH) is a common autosomal dominant condition characterized by severely elevated levels of serum cholesterol and associated with early atherosclerosis and premature coronary heart disease (CHD) [1]. Most cases are caused by mutations within the LDL receptor gene that decreases its proper function and results in high levels of plasma low-density lipoprotein (LDL) cholesterol [2]. There are two types of familial hypercholesterolaemia: heterozygous (He) FH, which affects between 1 in 200 to 1 in 500 people, and homozygous (Ho) FH, which occurs with the prevalence as high as one in 160,000 to 300,000 subjects [3–5]. The prevalence of FH in certain ethnic groups could be even higher [6]. Approximately 20 million people are affected by FH worldwide [7]. FH is widely underdiagnosed and undertreated as about three quarters of cases are undetected until middle age [8,9]. This represents a major problem, as at least 50% of men with FH will develop CHD by the age of 50 and women with FH have a 30% risk of CHD by the age of 60 years [10].

Early lipid-lowering treatment has been proved to be effective, so early identification of affected individuals is very important [11]. FH meets the criteria for systematic screening according to World Health Organization (WHO) as well as National Lipid Association recommendations of universal screening for elevated serum cholesterol, but only a few countries have established national

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screening programmes so far [12,13]. The screening for FH seems crucial as the disorder is highly prevalent, associated with premature death and has effective treatment options. Currently, no universal consensus on diagnostic criteria for FH exists, as there are three different sets of criteria used worldwide: Simon Broome Registry [14], the Make Early Diagnosis-Prevent Early Death (MEDPED) [15] and Dutch Lipid Clinic Network (DLCN) [16]. All criteria include both LDL-cholesterol levels and family history and can be used to establish diagnosis of FH.

Cardiovascular diseases (CVD) is a major cause of premature death in Lithuania as more than half of all deaths (56.2%) were caused by CVD in 2016 [17]. Dyslipidaemia is a very frequent cardiovascular risk factor in our country since it is diagnosed in nine out of ten middle-aged adults in primary care settings [18]. Therefore, the prevalence of FH in our country could be even higher than estimated worldwide [19]. In 2017, the nationwide FH screening programme has been started in Lithuania, which is extremely necessary for efficiently detecting, monitoring and treating patients with FH. After identifying the individual with FH by opportunistic screening, cascade screening of relatives should be applied as a cost-effective approach to find patients with FH [20,21]. Evaluating the lipid profile of subjects in primary care settings can help identify the first individual diagnosed with FH in the family ("index case"), which is the initial goal in cascade screening approaches [22]. In this study, we first aimed to describe the methods currently applied to perform screening for possible FH and discover the "index cases" in Lithuania. Alert systems for specific LDL-C thresholds for FH in clinical laboratories have been shown to be effective [23,24] so we decided to screen available databases for extremely elevated LDL-C levels to find patients with likely FH phenotype and estimate the prevalence and detection rate of likely phenotypic FH in the Lithuanian population using the LDL-C cut-off values that align with DLCN criteria. In this study, we present Lithuania's efforts to establish a national FH screening programme and discuss its further development to effectively identify, monitor and treat patients with FH.

2. Materials and methods

2.1. Establishing a national FH screening programme in Lithuania

While establishing a national FH screening programme, Lithuania started to participate in various national and international initiatives associated with FH: Competence centre of Lipidology in Vilnius university hospital (VUH) Santaros Klinikos (member of MerabERN), Vascular Research Network, EUROASPIRE, the EAS-FHSC network, ScreenPro FH project. National FH screening programme is promoted by the National Health Insurance Fund, the Programme for Rare Diseases and Pharmaceutical companies. The project of long-term monitoring of patients with FH over the age of 18, as a part of the European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration (EAS-FHSC) initiative, is waiting for the Regional Biomedical Research Ethics Committee's approval and it is expected to be started at the end of May 2018. The coordinating centre of the FH registry was set to be the tertiary care hospital with specialized cardiovascular prevention unit – VUH Santaros klinikos. When developing the network of care for subjects with FH, several collaborating centres are planned to be included. In our country, children and adolescents under the age of 18 are supervised by general practitioners (GPs) and pediatricians, so children with FH are referred to Coordinating Centre for Children Rare Diseases at the Children Hospital, affiliate of VUH Santaros klinikos (one of the collaborating centres of this project). Younger adults and children are under-represented in the screening programme, although they may be found by cascade screening process of index cases. We chose the opportunistic screening approach guided by increased levels of LDL-cholesterol as our main method to detect the possible index cases in general population.

2.2. Patients

The identification of potential FH patients was performed by several approaches:

1. An electronic extraction tool was applied to the database of lipidograms of the Lithuanian High Cardiovascular Risk (LitHiR) primary prevention programme. This programme was started in 2006 for the identification of high-risk patients, estimation and aggressive managing of cardiovascular risk factors in Lithuania. It includes 40–54 years old men and 50–64 years old women without overt CVD from all Lithuanian regions. The two-level approach including primary health care institutions and specialized cardiovascular prevention units is applied. The subjects with high cardiovascular risk examined in primary care level are sent to specialized prevention units. 398 out of 420 (94.8%) primary health care centres throughout all Lithuanian regions provide information of examined subjects in the LitHiR electronic database. Screening is performed on more than 200000 middle-aged subjects every year. In 2016, 256625 adults were examined, covering about 37,5% of all target population. The LitHiR programme consists of subjects selected in three different ways: enrolling the patients of a particular age who visit primary health care institutions, inviting adults who fit the programme inclusion criteria after the evaluation of their medical records and informing people about the programme through mass media [25]. The exclusion criteria are: a) proven coronary heart disease, b) proven cerebrovascular disease, c) proven peripheral artery disease, d) end-stage oncological disease, e) any other end-stage somatic disease. Participants included in the programme in primary care settings undergo a physical examination, assessment of their risk factors, family history evaluation and various instrumental and laboratory investigations, including lipid profile assessment. This programme was chosen as a basis for national screening programme as it contains large database of lipidograms convenient to opportunistically screen for people at high risk for FH. A detailed description of the Lithuanian primary prevention programme protocol is provided in the article by Laucevicius et al. [25]. During the period of 2009–2016, more than 1600000 examinations of middle-aged Lithuanians were made and 92373 lipidograms included in the LitHiR electronic database were screened for likely phenotypic FH.
2. Screening of the lipid profiles of adults with early onset CVD was applied in VUH Santaros klinikos electronic database (ELI). Young (<50 years) Lithuanian adults with the diagnosis of coronary heart disease (unstable angina, stable angina and myocardial infarction) who were treated in the tertiary care hospital during the period of 2005–2016 were evaluated. These patients are treated and monitored in secondary prevention unit in VUH Santaros Klinikos and the medical records of these subjects are available in ELI accessible only to delegated users. Medical records of 1714 young adults were screened for likely phenotypic FH.
3. Subjects with high cardiovascular risk referred from primary care institutions to the specialized cardiovascular prevention unit in VUH Santaros klinikos were screened for likely phenotypic FH. Patients with high cardiovascular risk are defined according to the European Society of Cardiology (ESC) guidelines on Cardiovascular Disease Prevention [26]. High-risk subjects