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Detection of familial hypercholesterolemia in patients from a general practice database

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Abstract

Objectives: Familial hypercholesterolemia (FH) is the most common monogenic lipid disorder associated with premature coronary heart disease. Early cholesterol-lowering therapy could effectively reduce cardiovascular disease morbidity and mortality in these patients. However, the majority of people with FH are undiagnosed, also due to low awareness and knowledge of FH in general practice, despite the high number of contacts GPs have with most of their patients which allows a systematic and effective approach to the detection of this condition. Here, we present a simple method to improve detection and to enhance awareness of FH in primary care using GP electronic health records.

Methods: We used electronic data from the Co.S. Consortium, involving more than 600 Italian affiliated GPs. Electronic data include demographic information, laboratory test results, recorded history of vascular disease and prescription of an HMG-CoA reductase inhibitor class medication. We performed a partial assessment of the Dutch Lipid Clinic Network (DLCN) score using those data that were recorded or available. We also sought to determine the prevalence of possible FH based on age-specific LDL-cholesterol thresholds employed by the diagnostic criteria of MEDPED and the non-age adjusted cut-off point (LDL-C $\geq$190 mg/dL).

Results: Data on LDL-C were available for 162,864 subjects. Mean LDL-C levels (SD) were 124.3 (33.6) mg/dL for non-treated subjects and 106.4 (38.5) mg/dL for statin-treated subjects. The cut-off of LDL-C $\geq$190 mg/dL yielded a prevalence of 2.9% among non-treated subjects and of 3.5% among statin-treated patients. Using the cut-off of $\geq$250 mg/dL, the prevalence was 0.1% among non-treated subjects and 0.3% among statin-treated patients. Using the cut-off $\geq$330 mg/dL (suggesting a probable diagnosis of FH according to the DLCN score) the prevalence was 0.01% and 0.02%. According to the stratification proposed by MEDPED criteria for the general population, the age-specific LDL-cholesterol thresholds identified 0.7% among non-treated subjects and 18.5% among statin-treated patients.

Conclusion: The diagnosis of FH is possible in general medicine and should be an integral part of the GP's activity.

Keywords: Cardiovascular diseases; Familial hypercholesterolemia; Primary healthcare

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1. Introduction

Plasma cholesterol levels are controlled by genetic and environmental factors. Primary or familial dyslipidemias are inherited diseases caused by a single genetic mutation in one of several genes. Genetic abnormalities that lead to abnormal blood lipid levels are mainly found in genes involved in the transportation and cellular uptake of lipids. Individuals who have these mutations often have severely abnormal blood lipid levels, which results in early-onset cardiovascular disease [1].

One of the most frequent forms is familial hypercholesterolemia (FH), an inherited disease in which genetic alteration results in the increase of low-density lipoprotein cholesterol (LDL-C) levels [2]. The frequency of heterozygous FH is estimated at about 1:200−1:250 in the general population [3−6], resulting in one of the most common monogenic disorders. The homozygous form (HoFH) is very rare, with an estimated rate of 1:1,000,000 people [7]. Individuals with heterozygous FH (HeFH) have total cholesterol and LDL-C plasma levels between 300 and 500 mg/dL (7.75−13 mmol/L). In HoFH, these levels are significantly higher (600−1200 mg/dL; 15.5−31.0 mmol/L).

Early diagnosis of FH is crucial because the disease should be early treated with lipid-lowering therapy and lifestyle changes to prevent cardiovascular complications [8,9]. In Italy, it has been estimated that <1% of cases are actually recognized and there is a general lack of uniform public health initiatives specifically directed to close the gap of knowledge on FH [5].

The frequency and clinical significance of these conditions justify a major effort to identify affected individuals and their families, a task entrusted almost entirely to general practitioners (GPs). In fact, the high number of contacts by GPs with most of patients allows a systematic and effective approach to the detection of this condition [10]. In a context where systematic screening is not applied, in addition to cascade screening after the identification of an index patient, opportunistic screening through the routinely clinical practice is the only opportunity to identify FH patients. Here, we present a simple method to improve detection and to enhance awareness of FH in primary care using GP electronic health records (GP EHR).

2. Methods

We used electronic data from the Consorzio Sanità − Co.S. (see Appendix). Data were collected by more than 600 Italian GPs affiliated with the Consortium, who in their daily clinical practice periodically extracted data which, after anonymization, were collected in the "My Search" database.

Electronic data include demographic information, laboratory test results, recorded history of vascular disease and prescription of an HMG-CoA reductase inhibitor class (statin) medication.

We performed a partial assessment of the Dutch Lipid Clinic Network (DLCN) score using those data that were recorded or available. The DLCN score includes assessment of: raised cholesterol and LDL-C concentrations, clinical characteristics (such as peripheral vascular disease; coronary artery disease), presence of tendon xanthoma or arcus cornealis, and a family history of premature heart disease [11]. The data extracted did not contain family history or examination findings, therefore the partial DLCN score assessment only included LDL-C concentrations and, where recorded, a personal history of vascular disease. The score determines the likelihood of an FH diagnosis as unlikely (<3 points), possible (3−5 points), probable (6−8 points), or definite (>8 points) FH.

We also sought to determine the prevalence of possible FH based on age-specific LDL-cholesterol thresholds employed by the diagnostic criteria of MEDPED [12] and the non-age adjusted cut-off point (LDL-C ≥190 mg/dL) adopted by the Italian Medicines Agency (AIFA) to regulate reimbursement of lipid lowering drugs in Italy, together with personal or familial history of premature coronary artery disease or tendinous xanthomata.

Descriptive statistics were calculated to describe patient characteristics. All analysis and results were completed in IBM SPSS Statistics version 23.

3. Results

Data on LDL-C were available for 162,864 subjects. Among them, 22.9% were on statin treatment. Mean LDL-C levels (SD) were 124.3 (33.6) mg/dL for non-treated subjects and 106.4 (38.5) mg/dL for statin-treated subjects. The serum LDL-C distribution for non-treated and statin-treated subjects is shown in Fig. 1A and B, respectively. The median serum LDL-C concentrations were 123.4 mg/dL. The 95th and 99th percentiles for serum LDL-C were 180.4 and 207.8 mg/dL, respectively.

The cut-off adopted by the Italian Medicines Agency of LDL-C ≥190 mg/dL yielded a prevalence of 2.9% among non-treated subjects and of 3.5% among statin-treated patients. Importantly, this last value is likely to be underestimated, as calculated on LDL-C levels reduced due to the lipid-lowering therapy. Assuming an average 30% reduction in LDL-C achieved by statin therapy and back-calculating hypothetical pre-treatment levels, the application of this cut-off would identify 20.8% of treated subjects (7.0% of the total sample).

If we considered the most recently estimated prevalence of FH in the general population of 1:200−1:250 [13], the cut-off of LDL-C in this population of untreated subjects would be 218 and 222 mg/dL, respectively.

The cut-off of 190 mg/dL also corresponds to the lowest threshold for the stratification of the levels of LDL-C