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Identification and characterization of severe familial hypercholesterolemia in patients presenting for cardiac catheterization

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BACKGROUND: Patients with severe familial hypercholesterolemia (FH) are often unrecognized despite typical presentation. The introduction of PCSK9 inhibitors opens new therapeutic options and emphasizes the need for identification of severe FH patients.

OBJECTIVES: The objective was identification, characterization, and management of severe FH patients by screening of cardiac catheterization (CC) database.

METHODS: Retrospective analysis of CC database from 2002 to mid-2015 was performed for low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL (n = 2383). Severe FH was diagnosed if any prior LDL-C was ≥280 mg/dL, excluding secondary causes. Peak/current LDL-C levels and lipid-lowering therapies were evaluated. Initial attempt was made to detect relatives with FH according to identifying data and age-dependent LDL-C cutoffs.

RESULTS: Severe FH was identified in 54 of initial 2382 patients with CC LDL-C ≥130 mg/dL. Mean age at cardiovascular disease diagnosis was 45 years. Peak LDL-C was 280 to 464 mg/dL (median, 322). Coronary artery bypass graft surgery was performed in 26 patients (48%) and redo coronary artery bypass graft surgery in 5 patients (9%). Risk factors included obesity (33%), hypertension (59%), smoking (33%), and diabetes (24%). LDL-C reduction ≥50% of peak value was achieved in 56%, LDL-C <130 mg/dL in 32%, and LDL-C <100 mg/dL in 17% of patients. High-intensity statin plus ezetimibe was prescribed for 67%, high-intensity statin alone for 24%, and other lipid-lowering therapies for 9% of patients. Treatment intensity was directly associated with attainment of LDL-C goals. Matching probands' surnames and place of residency with district health maintenance organization database has identified 161 additional individuals with possible FH; 58% were not treated with lipid-lowering drugs.

CONCLUSIONS: A simple algorithm for identification of patients with severe FH was implemented based on large catheterization and health maintenance organization databases and revealed patients with severe FH and coronary disease at a young age, with low attainment of cholesterol treatment goals. Screening existing cardiovascular databases of populations at risk will promote identification and management of severe FH patients and their affected family members.

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Introduction

Familial hypercholesterolemia (FH), a common monogenic disorder of lipoprotein metabolism, is associated with high concentrations of low-density lipoprotein cholesterol (LDL-C), predisposing affected individuals and their families to premature coronary heart disease (CHD).[1] FH is prevalent globally, reaching 1:250 in the general population in its heterozygous form due principally to autosomal dominant inheritance.[2] Nevertheless, FH is vastly underdiagnosed and undertreated in most countries.[3]

A direct causal relationship exists between cholesterol and CHD, and the risk of clinical atherosclerosis and mortality in FH is correlated with the extent of LDL-C levels.[4–6] Cardiovascular risk is further driven by the presence of concomitant risk factors and the cumulative LDL-C burden throughout life, which is a function of age of initiation of drug therapy and compliance to treatment. Patients with "severe FH" are often unrecognized despite typical presentation with premature CHD and physical stigmata. Identification of severe FH patients is important, as early intensive treatment and cascade screening of families may further reduce cardiovascular event rates.

Although direct detection of causative gene mutations is available and molecular genetics for screening family relatives is carried out successfully in several countries, genetic testing is still costly and is not systematically feasible in most places. In addition, despite the cost-effectiveness of cascade screening as a method to identify people with FH, few countries have established large-scale programs to systematically diagnose FH, and in Israel, there is no national screening program for the disease.[7] Accordingly, additional methods to enhance identification and screening of severe cases of the disease are imperative.

Screening of cardiovascular medical databases may improve identification and management of severe FH patients. We aimed to retrospectively use our cardiac catheterization (CC) laboratory database to identify, characterize, and treat severe FH patients in the immediate future.

Materials and methods

Study population

We performed a retrospective analysis of the CC laboratory database at Carmel Medical Center, Haifa, Israel, between the years 2002 to mid-2015 to identify the most recent LDL-C level (routinely documented in the catheterization files) before each patient's first coronary angiogram. LDL-C levels were present in 10,719 patients. Subjects presenting for coronary angiography with LDL-C level ≥130 mg/dL (n = 2383) were screened for the presence of severe FH.

Severe FH was defined as any past documentation of LDL-C ≥280 mg/dL. Subjects with definite secondary causes of severe hypercholesterolemia, such as cholestasis, nephrotic syndrome, or severe hypothyroidism, were excluded from the final analysis. Patient characteristics including age at first diagnosis of CHD, comorbidities, and cardiovascular risk factors; peak vs most recent LDL-C levels; and current lipid-lowering therapies were evaluated. Rosuvastatin 20 to 40 mg/d and atorvastatin 40 to 80 mg/d were considered as high-intensity statin therapy. After the index coronary angiogram, patients were followed up through the online databases, and recurrent percutaneous coronary angiographies and coronary artery bypass graft surgery (CABG) were identified.

To identify additional FH individuals living in the area covered by our regional section of the major national health maintenance organization (HMO) (Clalit Health Services, Israel), initial screening for relatives of patients diagnosed with severe FH was performed. Index cases identifying information were matched with the regional HMO database. Because population mobility is low in this region, individuals with the same surname and area of residency could be identified with peak LDL-C levels above an approximate probability for FH of 80% in the setting of the general population: LDL-C ≥250 mg/dL in patients aged ≥30 years; ≥220 mg/dL for patients aged 20 to 29 years, and ≥190 mg/dL in patients <20 years.[8] Identified cases were defined as possible FH.

Utilization of the database of the CC laboratory was approved by the Lady Davis Carmel Medical Center institutional review board and regional HMO FH database by Clalit Health Services regional ethics committee.

Statistical analysis

Continuous data are presented as means ± standard deviation or median and interquartile range (IQR) and categorical variables as numbers and percentages. The independent-samples *t* test was used to compare continuous variables or the Mann-Whitney test for skewed data, and the chi-square test was used to compare categorical variables. The Fisher exact test was used in cases of small sample sizes. The results were considered statistically significant when the 2-sided *P* value was <.05. SPSS statistical software, version 20.0 (SPSS Inc., Chicago, IL), was used to perform all statistical analyses.

Results

Severe FH was diagnosed in 54 of the 2383 patients screened (prevalence 1:44 of screened patients; 20% female). All patients had documented CHD. Mean age at initial diagnosis of CHD was 44 ± 11 years in men and 50 ± 11 years in women (range, 27–67 years; Fig. 1); CHD was diagnosed before the age of 50 years in 72% of the men and 45% of women. Peak LDL-C ranged between 280 and 464 mg/dL (median, 322; IQR, 295–349). Concomitant cardiovascular risk factors during index hospitalization