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Original Article

The very high cardiovascular risk in heterozygous familial hypercholesterolemia: Analysis of 734 French patients

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BACKGROUND: Heterozygous familial hypercholesterolemia (heFH) is a genetic disease causing high levels of low-density lipoprotein cholesterol (LDL-C). Although this population is at high cardiovascular (CV) risk, the risk is variable within patients depending on additional risk factors. CV disease risk groups have been defined by the Nouvelle Société Francophone d'Athérosclérose (NSFA) and by the National Lipid Association recommendations.

OBJECTIVES: The study aimed to describe a sample of French heFH patients, comparing patients at very high risk (VHR) and patients at high risk in terms of demographic and clinical characteristics as well as biological measurements and disease management.

METHODS: Cross-sectional retrospective analysis on 734 patients hospitalized after 2005 in 5 academic centers.

RESULTS: When considering NSFA classification, 550 (74.9%) patients belonged to the VHR group. Most patients in the VHR group presented more than 1 risk factor, the most prevalent ones being Lp(a) $>$ 50 mg/dL and smoking. Patients in the VHR group were older (50.6 vs

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45.0 years old, $P = .0002$), and presented a higher body mass index (25.5 kg/m^2 vs 23.3 kg/m^2, $P < .0001$). The proportion of patients with carotid arterial plaque was higher in the VHR group (59.8% vs 48.6%, $P = .06$). Total cholesterol (2.41 g/L on average) and LDL-C (1.65 g/L on average) were not found to be significantly different. Maximum level of lipid-lowering treatments were used in 34% of cases in the VHR group, significantly higher than 16% in the high-risk group ($P = .001$). Very similar results were found when using the National Lipid Association recommendations.

CONCLUSION: This study provides a detailed description of French heFH patients according to their CV risk. Patients with very high CV risk had usually more advanced carotid plaques and were treated with heavier lipid-lowering drugs although their LDL-C level remained similar. This highlights the significant burden of this population.

Introduction

Familial hypercholesterolemia (FH) is an autosomic dominant hereditary disease, caused by mutations in genes involved in the low-density lipoprotein cholesterol (LDL-C) catabolism: LDLR, APOB, and PCSK9. The prevalence of the heterozygous form (heterozygous familial hypercholesterolemia [heFH]) has been estimated between 1/250 and 1/500 and affects all ethnics, with founder effect in some countries.[1] In heFH patients, LDL-C levels are genetically elevated because fetal life and the long-term exposure of the arteries to high level of blood cholesterol lead to premature atherosclerosis.

An LDL-C level superior to 1.90 g/L in adults and superior to 1.60 g/L in children observed on 2 distinct lipid profiles should trigger suspicion of heFH.[2] Extravascular deposits of cholesterol include tendon xanthomas, xanthelasmas, and arcus senilis. Nevertheless, heFH often goes unnoticed because its clinical expression is almost nonexistent before the first cardiovascular (CV) episode. This first CV episode is often premature in untreated patients, before the age of 50 years for men and before the age of 60 years for women.[3] Dutch lipid clinic criteria is a composite score used in Europe allowing to classify patients in probability groups of being a case of heFH, from possible to definite diagnosis, using family history of early CV event or very high LDL-C level, clinical history, clinical examination, biological assessment, and genetic testing results.[4] Genetic testing can offer an accurate definite diagnosis of FH.[5] Genetic testing when patients have a family history of early CV events or of very high cholesterol levels (called cascade family testing) and clinical testing in other patients is a cost-effective method of identifying patients with heFH.[6]

Once the diagnosis of heFH has been output, therapeutic management consists of lifestyle modifications (smoking cessation, lose weight, physical activity, and low-cholesterol diet) and a lifelong drug treatment (statins for all FH patients and high doses of statins in adults).[2]

Compared with patients with commune polygenic hypercholesterolemia, patients with heFH have higher risk of CVD because of the length of exposition to high LDL-C levels.[7] Consequently, the use of regular CV risk stratification algorithms such as the Framingham or SCORE equations are not recommended in heFH patients, as they underestimated the CV risk.[8–10]

All heFH patients are considered to be at high CV risk, but the risk within FH is variable, and some patients may be at very high CV risk depending on other associated CV risk factors. No risk categorization of heFH patients has been internationally accepted, and several categorizations have been output in the literature, such as Nouvelle Société Francophone d'Athérosclérose's (NSFA), the National Lipid Association (NLA) recommendations, or more recently, the Spanish consensus article.[2,11–13] There is no external validation of such definitions, either on vascular burden or on risk to develop CV disease. However, severe heFH patients should be identified because they are susceptible to need a closer follow-up than other FH patients.[2,11,12,14,15]

Currently, no epidemiologic study has yet described heFH population with very high risk (VHR) of CV events in France. This study provides an explanatory description of these patients: the objectives are to identify patients belonging to the VHR group for heHF according to NSFA recommendations in a French cohort of heFH patients and to describe their risk factors, as well as demographic, clinical, biological, and therapeutic characteristics.

Methods

Source of data

NSFA collected information on patients with heFH who visited a lipid clinic between 1988 and 2011, in one of 5 academic French centers (Paris, Lille, Dijon, Nice, and Lyon), to measure changes in LDL-C levels and to evaluate if patients achieved their LDL-C targets. Some analyses on this database have already been published in peer-reviewed literature.[16] The main objective of this previous observational study was to describe changes in LDL-C levels of patients over time and evaluate their LDL-C target achievement.