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Phenotype diversity among patients with homozygous familial hypercholesterolemia: A cohort study

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ABSTRACT

Aims: Homozygous familial hypercholesterolaemia (HoFH) is a rare disorder usually caused by mutations in both alleles of the low-density lipoprotein receptor gene (*LDLR*). Premature death, often before the age of 20 years, was a common fate for patients with HoFH prior to the introduction of statins in 1990 and the use of lipoprotein apheresis. Consequently, HoFH has been widely considered a condition exclusive to a population comprising very young patients with extremely high LDL cholesterol (LDL-C) levels. However, recent epidemiologic and genetic studies have shown that the HoFH patient population is far more diverse in terms of age, LDL-C levels, and genetic aetiology than previously realised. We set out to investigate the clinical characteristics regarding age and LDL-C ranges of patients with HoFH.

Methods and results: We analysed the data from 3 recent international studies comprising a total of 167 HoFH patients. The age of the patients ranged from 1 to 75 years, and a large proportion of the patients, both treated and untreated, exhibited LDL-C levels well below the recommended clinical diagnostic threshold for HoFH. LDL-C levels ranged from 4.4 mmol/L to 27.2 mmol/L (170–1052 mg/dL) for untreated patients, and from 2.6 mmol/L to 20.3 mmol/L (101–785 mg/dL) for treated patients. When patients were stratified according to *LDLR* functionality, a similarly wide range of age and LDL-C values was observed regardless of *LDLR* mutation status.

Conclusion: These results demonstrate that HoFH is not restricted to very young patients or those with extremely high LDL-C levels.

1. Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare but serious genetic disorder. The condition is caused by mutations in both alleles of the low-density lipoprotein receptor gene (*LDLR*), resulting in severe hypercholesterolaemia (15–25 mmol/L or 600–1000 mg/dL). By virtue of the extremely elevated low-density lipoprotein cholesterol (LDL-C) levels, patients with HoFH typically suffer from clinical coronary heart disease manifestations in childhood that frequently lead to death before the age of 20 years [1]. In 2001, Goldstein et al. reported that HoFH affects one in one million individuals. However, recent data from studies in unselected general population samples suggest that the prevalence of HoFH may have been underestimated [2,3]. The Copenhagen General Population Study estimated an HoFH prevalence of approximately one in 160,000 in an unselected European general population sample, and a recently published study using data from a nationwide diagnostic center for autosomal dominant hypercholesterolaemia (ADH) in the Netherlands found an HoFH prevalence of one in 300,000 based on molecular diagnosis (this prevalence includes some patients with homozygous apolipoprotein B gene [*APOB*] mutations) [2,3]. Higher rates of HoFH have also been observed in certain populations where a founder effect or high rates of consanguinity are present (e.g., French Canadians in Quebec, Lebanese, South African Afrikaners) [1].

While the original definition of HoFH by Goldstein and colleagues has persisted, the disease is now considered to have a more diverse

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aetiology, with the recognition of autosomal dominant forms arising not only from mutations in the *LDLR* gene, but also from rare mutations in the *APOB* gene and gain-of-function mutations in the proprotein convertase subtilisin/kexin type 9 gene (*PCSK9*). Very rarely, HoFH can be inherited as a recessive condition known as autosomal recessive hypercholesterolaemia (ARH), which is the result of mutations in the gene encoding LDL receptor adaptor protein 1 (*LDLRAP1*) [4–8]. Moreover, HoFH, as it is molecularly defined, may now include patients who are double heterozygotes (those possessing mutations in two or more of the implicated genes) and compound heterozygotes (those possessing different mutations in both alleles of one of the implicated genes). These double heterozygotes and compound heterozygotes present with the HoFH phenotype but exhibit more variable low-density lipoprotein cholesterol (LDL-C) levels and, in general, have a lower risk for atherosclerotic disease [4].

The diagnostic criteria for HoFH have been inconsistent in the literature. Table 1 in the Data in Brief file associated with this publication lists the criteria endorsed by the European Atherosclerosis Society (EAS) Consensus Panel on Familial Hypercholesterolaemia [5,9]. The criteria used in this update include a substantial downward adjustment in threshold LDL-C levels compared with the definition by Goldstein et al. [1].

Patients with HoFH are generally considered to be very young. A South African cohort of patients with HoFH, studied prior to the availability of statins in 1990, had a mean age of death that was approximately 18 years. However, after the availability of statins in 1990, the mean age of death had been extended to approximately 33 years. The mean LDL-C level with the use of statins in this cohort was still quite elevated at 11.7 ± 3.4 mmol/L (452 ± 131 mg/dL) [10]. The high levels of LDL-C are typical for patients with HoFH and represent the fundamental dysfunction resulting in an elevated risk of atherosclerotic cardiovascular disease. Deposition of cholesterol in patients with HoFH is proportional to the cholesterol-year score—a combined measurement of hypercholesterolaemia severity and duration—underscoring the relationship between LDL-C and cardiovascular risk [5]. Furthermore, LDL-C is, in general, inversely proportionally correlated with *LDLR* activity, as evidenced by a study in 32 Italian patients with HoFH, for whom a negative correlation between LDL-C and residual *LDLR* activity was observed ($r = -0.66$; $P < 0.003$) [11].

The expansion of the definition of HoFH, based upon improved sources of patient data and advances in genetic research, led us to re-examine longstanding assumptions about the presentation, prevalence, and distribution of HoFH. The purpose of the present study is to describe the manifestations and characteristics of HoFH, with a particular focus on the phenotypic variables of patient age and range of LDL-C values, by analysing data from three international studies published over the last few years describing diverse groups of patients with HoFH.

2. Methods

The first of the 3 studies used for the present analysis consists of the baseline data pertaining to patients enrolled in a phase 3, multicentre, international, randomised, double-blind, placebo-controlled trial (the Genzyme [GZ] HoFH study, ClinicalTrials.gov number NCT00607373, sponsored by Sanofi Genzyme) comparing treatment with mipomersen vs placebo in patients with HoFH [12]. It should be noted that the baseline LDL-C levels derived from this study reflect LDL-C levels prior to treatment with mipomersen. The second study is a published retrospective chart review of patients treated at two specialised lipid clinics in South Africa (SA study) between 1972 and 2009 [10]. The third study is the published analysis of data derived from the national database of patients with HoFH in the Netherlands, compiled by the Academic Medical Center in Amsterdam (AMC study), a nationwide DNA diagnostic centre where patients in the Netherlands are referred for molecular diagnosis of FH [3].

2.1. Diagnostic criteria

Diagnostic criteria for HoFH used in the GZ HoFH study and SA study were identical, and largely mirror those of the EAS Consensus Panel: genetic confirmation of two mutant alleles at the *LDLR* gene locus or clinical diagnosis based on untreated LDL-C levels >13 mmol/L (500 mg/dL) in addition to either xanthoma(s) observed before 10 years of age or evidence of heterozygous FH in both parents [10,12]. Diagnostic criteria for the AMC study involved confirmation of pathogenic mutations for autosomal-dominant FH, specific to monogenic manifestations [3].

2.2. Exclusion criteria

Subjects meeting the following criteria were excluded: (1) subjects actively undergoing lipoprotein apheresis, (2) subjects with genetic confirmation of a form of HoFH that did not directly involve the *LDLR* gene (e.g., *APOB*), and (3) subjects who were deceased.

2.3. Phenotypic assessment

LDL-C levels were obtained at each centre from medical records. Untreated LDL-C (uLDL-C) refers to the LDL-C level prior to initiation of lipid-lowering therapy (LLT). Treated LDL-C (tLDL-C) refers to the LDL-C level while the patient was taking the maximally tolerated available LLT.

Patient age in the GZ HoFH study cohort was derived from the case report forms at baseline enrollment. Patient age in the AMC cohort was published online as supplemental data to the original publication [3]. To be consistent with the GZ HoFH cohort, a conservative age was used for patients in the SA lipid clinics, based on the year that enrollment began in the GZ HoFH study (i.e., 2007) instead of using patient age at the time of this analysis.

2.4. Molecular assessment

Molecular assessment was undertaken based on classification of *LDLR* mutations into one of six categories: (1) defective/defective, (2) defective/negative, (3) negative/negative, (4) defective/unclassified, (5) negative/unclassified, or (6) unclassified/unclassified. An LDL receptor mutation designated as “negative” is associated with <2% of LDL uptake in cultured fibroblasts; a receptor mutation designated as “defective” is associated with 2%–25% of normal uptake [13]. If the receptor status was not reported or was unknown in the study publication, it was considered to be unclassified.

2.5. Atherosclerotic cardiovascular disease (ASCVD)

We defined ASCVD as any documented history of coronary artery disease (CAD), aortic valve replacement or repair (AVR), carotid disease, or peripheral vascular disease. Additionally, we defined CAD as any general designation in the medical history or if myocardial infarction, angina pectoris, acute coronary syndrome, or coronary artery bypass graft (CABG) surgery were specifically mentioned.

2.6. Comparative assessment

The diagnostic methodologies of the SA and GZ HoFH studies were similar, involving initial clinical identification of patients (i.e.,