Atherosclerosis 260 (2017) 67–74

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Significance of lipoprotein(a) levels in familial hypercholesterolemia and coronary artery disease

Sha Li [1], Na-Qiong Wu [1], Cheng-Gang Zhu, Yan Zhang, Yuan-Lin Guo, Ying Gao, Xiao-Lin Li, Ping Qing, Chuan-Jue Cui, Rui-Xia Xu, Jing Sun, Geng Liu, Qian Dong, Jian-Jun Li*

Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Peking Union Medical College, BeiLiShi Road 167, Beijing 100037, China

ARTICLE INFO

Article history:
Received 16 December 2016
Received in revised form
9 March 2017
Accepted 16 March 2017
Available online 18 March 2017

Keywords:
Familial hypercholesterolemia
Lipoprotein (a)
CAD
Early-onset

ABSTRACT

Background and aims: Patients with familial hypercholesterolemia (FH) are often characterized by premature coronary artery disease (CAD) with heterogeneity at onset. The aim of the present study was to investigate the associations of lipoprotein (a) [Lp(a)] with the FH phenotype, genotype and roles of Lp(a) in determining CAD risk among patients with and without FH.

Methods: We enrolled 8050 patients undergoing coronary angiography, from our Lipid clinic. Clinical FH was diagnosed using the Dutch Lipid Clinic Network criteria. Mutational analysis (*LDLR*, *APOB*, *PCSK9*) in definite/probable FH was performed by target exome sequencing.

Results: Lp(a) levels were increased, with a clinical FH diagnosis (unlikely, possible, definite/probable FH) independent of the patients status, with Lp(a)-hyperlipoproteinemia [Lp(a)-HLP] (median 517.70 *vs.* 570.98 *vs.* 604.65 mg/L, $p < 0.001$) or without (median 89.20 *vs.* 99.20 *vs.* 133.67 mg/L, $p < 0.001$). Patients with Lp(a)-HLP had a higher prevalence of definite/probable FH than those without (6.1% *vs.* 2.4%, $p < 0.05$). However, no significant difference in Lp(a) was observed in patients with definite/probable FH phenotype carrying *LDLR* or LDLR-independent (*APOB*, *PCSK9*) or neither mutations ($p > 0.05$). Multivariate analysis showed that Lp(a) and FH phenotype were both significant determinants in predicting the early onset and severity of CAD. Subsequently, patients with Lp(a)-HLP in definite/probable FH increased significantly the CAD risk (all $p < 0.05$).

Conclusions: Lp(a) levels were higher in patients with FH phenotype than in those without, but no difference were found in FH patients of different mutated backgrounds. Moreover, Lp(a) and FH played a synergistic role in predicting the early onset and severity of CAD.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Familial hypercholesterolemia (FH) is characterized by an increased risk of premature coronary artery disease (CAD) mainly due to the life-long accumulation of low-density lipoprotein (LDL) cholesterol (LDL-C) [1]. Mutations in LDL receptor (LDLR) gene (*LDLR*), apolipoprotein B (apoB) gene (*APOB*), and proprotein convertase subtilisin/kexin type 9 (PCSK9) gene (*PCSK9*) are well-recognized causes of FH [2]. These mutations lead to functional or quantitative defects of proteins in the LDLR pathway, resulting in a severe hypercholesterolemia phenotype [2].

However, many subjects with FH phenotype are recognized to have no defects in these genes. For example, in patients classified as 'definite FH' using the Dutch Lipid Clinic Network (DLCN) criteria from a Danish population, the mutation detection rates ranged between 54 and 70% [3–5]. It is worth noting that a negative genetic test result does not exclude FH because many of the clinical FH may be caused either by mutations in genes yet to be identified or by polygenic, epigenetic or acquired defects [6,7]. Interestingly, several investigators point out that patients with FH have the same clinical consequence regardless of the genotype, and the cardiovascular risk is determined by life-long exposure to hypercholesterolemia, but not by the mutations that produce it [6,7]. Recent studies have indicated that for any given observed LDL-C level, CAD risk is substantially higher in FH mutation carriers than in non-carriers [8].

It is currently known that patients with FH have heterogeneity

* Corresponding author.
E-mail address: lijianjun938@126.com (J.-J. Li).
[1] These authors contribute equally to this work.

http://dx.doi.org/10.1016/j.atherosclerosis.2017.03.021
0021-9150/© 2017 Elsevier B.V. All rights reserved.

at the onset of CAD. In addition to the presence of FH mutations, certain risk factors including lipoprotein (a) [Lp(a)] have received increasing or re-waking interest concerning their contributions to CAD [9–12]. It may be due to the fact that individuals with clinically or genetically diagnosed FH have increased Lp(a) levels or that an independent causal role of Lp(a) in CAD has been established by a patient-level meta-analysis of prospective studies as well as a large Mendelian randomization evaluation [13–15]. Moreover, Lp(a) seems to be one of the residual risk factors for CAD in the statin era [16]. Novel therapeutic agents, which can significantly lower Lp(a) levels, have recently become available and some of them are undergoing clinical trials [17–19]. Studies with these agents will hopefully provide more direct information on whether reductions in Lp(a) levels decrease events independently of LDL-C [17–19].

Accordingly, the primary aim of the present study was to provide data concerning the role of Lp(a) levels in relation to FH phenotype, as well as genotype, and compare the effect of Lp(a) on CAD risk in patients with or without clinical FH. Along with evaluating the primary hypothesis, the study was designed to answer the following questions: (1) did patients with Lp(a) at low levels (<300 mg/L) significantly contribute to FH phenotype, as well as those at an elevated level (≥300 mg/L)? (2) were there any differences in Lp(a) levels among FH patients of different mutated backgrounds? (3) what an elevated Lp(a) level mattered in predicting the early-onset or severity of CAD in patients with or without FH?

2. Materials and methods

2.1. Study population

Our study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Fu Wai Hospital & National Center for Cardiovascular Diseases, Beijing, China). Informed written consent was obtained from each patient enrolled in this study. From March 2011 to March 2016, we consecutively recruited those subjects from our Lipid clinic, who were referred for coronary angiography (CAG), due to suspected CAD. Patients with significant hematologic disorders, infectious or systematic inflammatory disease, thyroid dysfunction, severe liver and/or renal insufficiency and malignant disease were excluded. As a result, a total of 8050 participants were enrolled at the time of the analysis.

2.2. Laboratory examinations

Blood samples for laboratory examinations were obtained from the cubital vein after a 12-h overnight fast. The concentrations of plasma total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), LDL-C, apolipoproteinA-I (apoAI), apoB and Lp(a) were measured using an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan). Of them, apoA-I and apoB levels were determined by turbidimetric immunoassay; Lp(a) levels were assayed by an immunoturbidimetry method according to the manufacturer's guide, a latex turbidimetric method [LASAY Lp(a) auto; SHIMA laboratories] with its normal reference value less than 300 mg/L.

2.3. Diagnostic criteria of FH and CAD

The diagnosis of clinical FH was established using the DLCN criteria as reported previously [3]. We did not employ the criteria relating to corneal arcus and molecular genetic testing to define FH in the algorithm. The diagnosis of CAD was finally defined as the presence of coronary lesions ≥50% in at least one major epicardial artery segment assessed by CAG. A group of 6749 patients were identified as CAD, with 3045 premature CAD (pCAD, or early-onset CAD, the onset-age of CAD <55 years for men, <60 years for women) and 3704 non-pCAD or later-onset CAD (the onset-age of CAD ≥55 years for men, ≥60 years for women). The severity of CAD was assessed according to Gensini score (GS) system [20]. The groups of patients with Lp(a)-hyperlipoproteinemia [Lp(a)-HLP] or without Lp(a)-HLP were divided by Lp(a) level of 300 mg/L. The groups of patients with high, median, low GS were divided by the tri-sectional quantiles of GS. Patients presenting with the first tertile of GS (<18), the second tertile of GS (18–40) and the third tertile of GS(≥40) were defined as low GS, median GS and high GS, respectively.

2.4. Target exome sequencing and genotyping

Genomic DNA was isolated using a commercially available DNA extraction kit (Tiangen Biotech, Beijing, China). DNA purity was tested by calculating the ratio of absorbance at 260 nm to absorbance at 280 nm, using a NanoDrop 2000 Spectrophotometer (NanoDrop Technologies, Wilmington, DE). Genomic DNA was sheared using the CovarisTM system. The sample preparation used was the Truseq DNA Sample preparation Kit (Illumina, Inc, San Diego, CA).

We sequenced the exomes of *LDLR*, *APOB* and *PCSK9* by target exome sequencing. In-solution exome enrichment was performed using SureSelect Target Enrichment Kit (Agilent technologies, Inc, USA). The enriched DNA samples were sequenced using a Hiseq2000 Sequencing System (Illumina), for 101 cycles of sequencing per read, to generate paired-end reads including 100 bps at each end and 6 bps of the index tag. The functional effect of non-synonymous SNVs was assessed by the PolyPhen-2, Sorting Tolerant From Intolerant (SIFT) and MutationTaster. Combined Annotation Dependent Depletion (CADD), Dann and Eigen were used for predicting the deleteriousness of insertion/deletions variants.

2.5. Statistical analysis

The values are expressed as mean ± SD or median (interquartile range) for the continuous variables and number (percentage) for the categorical variables. Differences of variables among the groups were analyzed using one-way ANOVA analysis, Kruskal-Wallis H test or χ^2-test where appropriate. Univariate and multivariate regression analyses were performed to investigate the associations of Lp(a), FH phenotype and CAD status. Odds ratio (OR) and 95% confident interval (95% CI) were calculated. A general linear model was used to study the adjusted Lp(a) levels among groups of patients with different CAD status. A p-value <0.05 was considered statistically significant. The statistical analysis was performed with SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

The clinical characteristics of the patients according to FH phenotype and genotype are summarized in Tables 1 and 2, respectively.

A total of 8050 subjects [30.2% (n = 2432) patients with Lp(a)-HLP and 69.8% (n = 5618) patients without Lp(a)-HLP] were given a probability evaluation of clinical FH using the DLCN criteria. In this algorithm, 281 definite/probable FH, 1519 possible FH and 6250 unlikely FH patients were identified. However, it is reported that the mean cholesterol content of total Lp(a) mass is roughly 30%, which is co-measured in total and LDL-C measurements [12]. Given

Download English Version:

https://daneshyari.com/en/article/5599621

Download Persian Version:

https://daneshyari.com/article/5599621

Daneshyari.com