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Original Article

Interleukin-1 genotypes modulate the long-term effect of lipoprotein(a) on cardiovascular events: The Ioannina Study

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BACKGROUND: Lipoprotein(a) [Lp(a)] is a genetic risk factor for cardiovascular disease (CVD), and proinflammatory interleukin-1 (IL-1) genotypes may influence Lp(a)-mediated CVD events. The genotype IL-1(+) is associated with higher rates of inflammation than IL-1(−) genotype. Targeting IL-1β was recently shown to decrease CVD events independent of low-density lipoprotein-cholesterol levels.

OBJECTIVE: The objective of the study is to assess the modulatory effect of IL-1 genotypes on risk mediated by Lp(a)

METHODS: We assessed whether IL-1 genotypes modulate the effect of Lp(a) on major adverse cardiovascular events (cardiovascular death, myocardial infarction, and stroke/transient ischemic attack) and angiographically determined coronary artery disease (CAD). IL-1 genotypes and Lp(a) were measured in 603 patients without diabetes mellitus undergoing angiography. Major adverse cardiovascular events and CAD were assessed over a median of 45 months.

RESULTS: In multivariable-adjusted analysis, Lp(a) was associated with major adverse cardiovascular events (hazard ratio [HR] [95% confidence interval {CI}]: 2.95 [1.16–7.54], $P = .023$) and CAD (odds ratio [OR] [95% CI]: 1.84 [1.12–3.03], $P = .016$) comparing quartile 4 vs quartile 1. In Cox regression analysis, IL-1(+) patients with Lp(a) above the median (>9.2 mg/dL) had a worse event-free cumulative survival (HR [95% CI]: 3.59 [1.07–12.03], $P = .039$) compared to IL-1(−) patients with Lp(a) below the median. In IL-1(+) patients aged ≤60 years, Lp(a) was also associated with angiographically determined

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CAD (OR [95% CI]: 2.90 [1.07–7.86], $P = .036$) comparing quartile 4 vs quartile 1 but not IL-1(−) patients.

CONCLUSION: Proinflammatory IL-1(+) genotypes modulate the risk of Lp(a) long-term CVD events and CAD. These data suggest that the dual genetic contributions of elevated Lp(a) levels and IL-1(+) genotypes may identify younger subjects at particularly high risk for CVD events.

Introduction

Traditional risk factors are important in identifying persons at increased risk for cardiovascular disease (CVD) but do not fully explain global risk. For example, despite optimal secondary prevention strategies, including achieving very low low-density lipoprotein cholesterol (LDL-C) levels, significant residual CVD risk remains and most events are not prevented.[1,2] Significant variability also exists in the clinical expression of CVD among persons with similar risk factors. Finally, a sizable proportion of CVD risk may be accounted for by low frequency but cumulative genetic variations that are not fully described or understood.[3]

Based on a preponderance of epidemiological and genetic studies, Lp(a), whose plasma levels are primarily genetically determined,[4] is now established as an independent, causal risk factor for CVD.[5] Like other risk factors, Lp(a) has variable expression of CVD at different circulating level thresholds. Understanding the influences that modify the strength of risk factors may allow more rational and personalized therapy for patients at risk for CVD. In that regard, we have previously shown that the risk of Lp(a) on angiographically determined coronary artery disease (CAD)[6] and CVD events[7] was dependent on a second genetic influence, namely proinflammatory interleukin-1 (IL-1) genotypes. These effects were seen mainly in patients aged ≤60 years, consistent with strong genetic influences present lifelong in subjects presenting with CVD earlier in life. These IL-1 genotypes comprise 3 single-nucleotide polymorphisms in the *IL-1* gene cluster[8,9] and were a priori determined to be proinflammatory before being evaluated in CVD studies.

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial demonstrated that anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of LDL-C-level lowering.[10] However, although the inflammatory hypothesis was proven, the benefit was modest in the overall group, suggesting that specific subgroups, such as those at increased genetic risk mediated by Lp(a),[5] may predict the benefit of targeting the interleukin-1β pathway. This study was designed to validate the hypothesis that the risk of angiographically determined CAD and CVD events mediated by Lp(a), particularly in younger patients, is influenced by proinflammatory IL-1(+) genotypes.

Methods

Study population

This study enrolled 603 consecutive patients undergoing a diagnostic coronary angiography based on a clinical suspicion of CAD at the 2nd Department of Cardiology in the University Hospital of Ioannina and the Catheterization Laboratory of 1st IKA Hospital in Athens, from January 2010 to December 2012. Patients were between 18 and 90 years at entry (index coronary angiography) and of both genders. Patients with a history of any coronary revascularization procedure, severe valvular disease, congenital heart disease, cardiomyopathies, and those on hemodialysis were excluded. In addition, patients with diabetes mellitus were excluded to be able to compare to prior studies[6,7] where such patients were excluded because they are a very high–risk group that may mask other underlying relationships.

Study design

The study was prospectively designed to test the association of CAD with proinflammatory and prothrombotic biomarkers in relation to the presence of specific IL-1 genotype groups known to be associated with higher inflammatory responses. Consecutive patients referred for clinically indicated angiography to 1 cardiology catheterization group between January 2010 and May 2013 were enrolled. The study protocol was approved by the Ethics Committee at the University Hospital of Ioannina. The study complied with the Declaration of Helsinki and all participants provided written informed consent.

Parameters recorded in the study were derived from patient's medical history, physical examination, laboratory evaluations, and coronary angiography. All subjects underwent catheterization and coronary angiography according to the standard Judkins technique. Angiograms were assessed in multiple projections independently by 2 experienced operators, and a consensus was reached. Angiographically significant disease was defined as diameter stenosis >50% in any one major epicardial coronary artery.

Blood samples were drawn after an overnight fast and just before coronary angiography for stable coronary syndromes. In patients with unstable coronary syndromes, blood samples for determination of lipids levels and fasting glucose were drawn either before coronary angiography or