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Relationship between interleukin-1β and depressive disorder after acute coronary syndrome

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ABSTRACT

This study was aimed to investigate the effect of serum interleukin (IL)-1β in the depression trajectory after acute coronary syndrome (ACS) considering two IL-1β polymorphisms: −511C/*T* or +3953C/*T*. A total of 969 patients were evaluated within 2 weeks after ACS and of these, 711 were followed-up 1 year later. Depressive disorders were evaluated at baseline and 1 year after ACS, using the Mini-International Neuropsychiatric Interview. Serum IL-1β levels and IL-1β genotypes were investigated at baseline. Covariates on socio-demographic and clinical characteristics including depressive symptoms, cardiovascular risk factors, and current cardiac status were assessed. Depression during the acute ACS was significantly associated with the IL-1β levels and the −511*T* allele. The interaction of the IL-1β level with depression at baseline in the presence of the −511*T* allele was also significant. No associations were found with depression during the chronic ACS. For the +3953C/*T* genotype, there was no association with depression in either the acute or chronic phase. The IL-1β level and −511C/*T* genotype, separately or interactively, could be a biomarker for depressive disorder in the acute phase of ACS. Focused interventions for those with higher IL-1β level and −511*T* allele might reduce the risk of depressive disorder.

1. Introduction

Depression is frequently comorbid with acute coronary syndrome (ACS). Moreover, depression comorbid with ACS predicts a poor prognosis (Lichtman et al., 2014). Mechanisms responsible for the link between depression and ACS have been investigated, and the inflammation hypothesis has been highlighted. Inflammation is associated serotonergic disturbances and hypothalamic–pituitary–adrenal axis hyperactivity, and inflammatory processes are involved in the pathophysiology of depression (Maes et al., 2011a; Lee et al., 2013). Furthermore, the role of inflammation in the pathogenesis and risk prediction of ACS has been well-established (Libby and Theroux, 2005), and the magnitude of the inflammatory response during ACS predicts cardiac outcomes (Berton et al., 2009). In short, inflammation is associated with depression and ACS separately (Maes et al., 2011b) as well as with a poor prognosis in ACS (Poole et al., 2011). In this context, previous studies have suggested a significant association between depression in ACS and inflammatory markers, including C-reactive protein and cytokines (Wilkowska et al., 2015).

Interleukin (IL)-1β, a key pro-inflammatory cytokine that induces other cytokines production, is associated with a poor prognosis in ACS based on its role in atherosclerosis development (Miranda-Malpica et al., 2008). Studies have found that higher IL-1β levels in depressive/exhausted patients in ACS (Appels et al., 2000) and that escitalopram lowered IL-1β levels in ACS model rats (Bah et al., 2011). A recent *in vitro* study showed that IL-1β signaling was involved in the inflammatory cascade at the onset of depression in patients with ACS and that statin functioned as an anti-inflammatory agent by downregulating IL-1β (Ma et al., 2016). However, it is difficult to draw conclusions regarding these associations due to study limitations, including small number of subjects, cross-sectional designs, and the limited number of clinical studies. Moreover, IL-1β secretion is altered by IL-1β gene polymorphisms: individuals with −511*T* or +3953*T* secreted higher levels of IL-1β than did those with —511*C* or +3953*C* polymorphisms (Wang et al., 2007; Hedley et al., 2002). Therefore, this study investigated the effect of serum IL-1β in the depression trajectory after ACS considering two IL-1β polymorphisms: −511C/*T* or +3953C/*T*.

Abbreviations: IL, Interleukin; ACS, acute coronary syndrome; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition criteria; K-DEPACS, Korean DEPression in ACS study; MINI, mini international neuropsychiatric interview; CK-MB, creatine kinase-MB; BMI, body mass index; LVEF, left ventricular ejection fraction; EKG, electrocardiography; PCR, polymerase chain reaction.

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2. Materials and methods

2.1. Study outline and participants

This study was part of the Korean Depression in ACS (K-DEPACS) study, an observational prospective study of depression in ACS patients, approved by the Chonnam National University Hospital Institutional Review Board; detailed methods are described elsewhere (Kim et al., 2014). The recruitment procedure is shown in Fig. 1. From patients recently hospitalized with ACS ($n = 4809$) in the Department of Cardiology of Chonnam National University Hospital, 969 patients who met the eligibility criteria and agreed to both participation and phlebotomy comprised the baseline sample. Baseline assessments were made within 2 weeks after ACS to assess the acute phase of ACS. In total, 711 baseline patients were followed-up 1 year later at outpatient clinics. Study psychiatrists assessed the participants to identify major or minor depressive disorder using the Mini-International Neuropsychiatric Interview (MINI, Sheehan et al., 1998). All participants provided written informed consent for the K-DEPACS, which received ethical approval from the Chonnam National University Hospital Institutional Review Board.

2.2. Diagnosis of depressive disorder

Depressive disorder was diagnosed using the MINI, a structured diagnostic psychiatric interview for DSM-IV defining major and minor depressive disorder categories as outputs (Sheehan et al., 1998). The interview has been translated and standardized in Korean (Yoo et al., 2006). Because ACS patients are generally discharged from the hospital within 2 weeks of intensive medical treatment, our diagnostic criteria for depressive disorder did not require a minimum symptom duration of 2 weeks at baseline; however, the standard 2-week symptom duration was required for diagnosis at follow up. Patients with major and minor depression were included in the study because there were too few patients with major depression to analyze separately. Assessments at baseline and 1-year follow up were used to evaluate depression status in the acute and chronic phases of ACS.

2.3. Serum IL-1β and polymorphisms

Serum IL-1β levels were analyzed using a solid-phase sandwich enzyme-linked immunosorbent assay kit (Invitrogen, Camarillo, CA, USA) and IL-1β genotypes were examined using polymerase chain reaction (PCR) and PCR-based restriction fragment length polymorphism assays. Considering the infrequency of +3953*T*/*T* genotypes, they were classified into two groups (*C*/*C or C*/*T*).

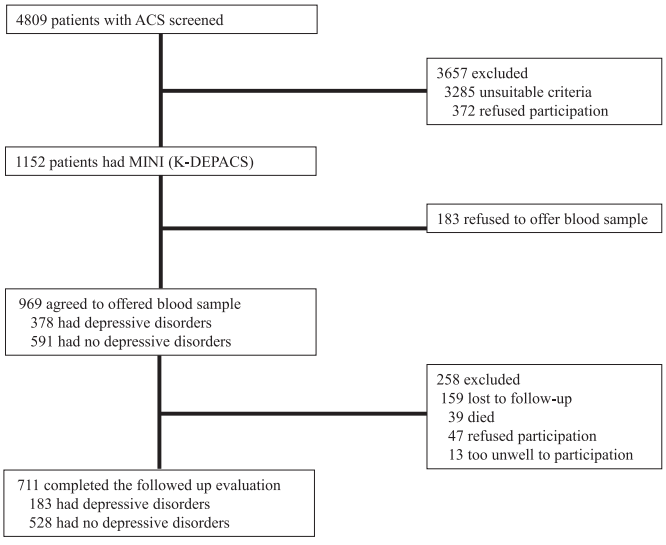

Fig. 1. Flow diagram for the recruitment procedure. ACS, acute coronary syndrome; MINI, Mini-International Neuropsychiatric Interview. K-DEPACS, Korean DEPression in Acute Coronary Syndrome study.

2.4. Demographic and clinical covariates

Factors that were likely to confound or mediate the association between depression and ACS were evaluated at baseline. Data on age, sex, level of education, living status (living alone or not), accommodation (owned or rented), current occupation (employed or not), and previous and family histories of depression were obtained. The following cardiovascular risk factors were determined: previous and family histories of ACS, diagnosis of hypertension or diabetes mellitus, hypercholesterolemia (defined as fasting serum total cholesterol level > 200 mg/dL), obesity (measured using body mass index), and reported current smoking status. Current cardiac status was estimated: the severity of ACS was assessed using the Killip classification (Killip and Kimball, 1967); left ventricular ejection fraction (LVEF) was assessed using echocardiography; and the serum cardiac biomarkers, troponin I and creatine kinase-MB, were measured. Another factor that could affect depression status at follow-up was treatment status, as patients diagnosed with depressive disorder at baseline were randomized to receive escitalopram or a placebo, or were treated with the usual medical care if they did not consent to participate in the study.

2.5. Statistical analyses

Using *t*-tests or χ^2 tests, the baseline variables, including sociodemographic data, depression characteristics, cardiovascular risk factors, and current cardiac status, were compared according to the baseline depressive status. Then, those characteristics with significant associations ($P < 0.05$) were considered as covariates in the multivariate analyses. According to the presence of depression at baseline and follow-up, the IL-1β levels and the two genotypes were compared using *t*-tests and χ^2 tests. To identify potential interaction effects, the associations of IL-1β levels with depressive status were initially stratified by the two genotypes. Then the interactions between the IL-1β levels and each genotype were analyzed using multivariate logistic regression models after adjusting for relevant covariates. Additionally, sensitivity analyses were performed after using the same methods to exclude participants with a history of depression. All analyses were performed using SPSS 18.0.

3. Results

3.1. Recruitment

Fig. 1 shows the recruitment procedure. In total, 969 (84.1%) of the K-DEPACS sample ($n = 1152$) consented to phlebotomy. The baseline characteristics of those who did and did not consent to phlebotomy did not significantly differ ($P > 0.15$ for all). Depressive disorder (major + minor) was diagnosed in 378 (39.8%) patients at baseline and in 183 (25.7%) patients at follow up. Follow-up evaluations were performed on 711 (73%) of the initial 969 participants at 1 year. Attrition ($N = 258$) was significantly correlated with increasing age and higher Killip class ($P < 0.05$ for both).

3.2. Serum IL-1β level and IL-1β genotype according to depression status

The baseline demographic and clinical characteristics of the 969 participants according to depression status are shown in supplemental Table S1. Female sex, lower education level, living alone, rented housing, current unemployment, presence of hypertension and diabetes, and current smoking were significantly associated with baseline depression (all $P < 0.05$). Table 1 presents the IL-1β levels and two genotypes by depressive status. ACS patients with depression at baseline had