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Short communication

Effects of interleukin-6, interleukin-18, and statin use, evaluated at acute stroke, on post-stroke depression during 1-year follow-up

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ABSTRACT

Proinflammatory cytokines are associated with the development of post-stroke depression (PSD). Statins are thought to possess anti-inflammatory properties but their interactions with cytokines regarding the risk of PSD have yet to be investigated. Thus, the present study aimed to determine whether interleukin (IL)-6 and IL-18 were associated with the development of depression at 2 weeks and 1 year after stroke using a longitudinal post-stroke cohort. Furthermore, this study examined the potential interactions between statin use and cytokines on PSD. For this study, 286 patients were evaluated 2 weeks after stroke and 222 patients were followed-up 1 year later. Depression was diagnosed using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and then categorized into no PSD or any PSD, which included diagnoses of both major and minor depression. The effects of IL-6 and IL-18 on PSD as well as their interaction with a statin at both examination time-points were investigated using a multivariate logistic regression model. Higher IL-6 and IL-18 levels were independently associated with depressive disorders within 2 weeks and at 1 year after stroke. When stratified by statin use, these significant associations were more evident in patients who did not use a statin. Furthermore, there was a significant interaction between statin use and IL-6 on the presence of a depressive disorder at 1 year. The present findings support the cytokine hypothesis of PSD and indicate that the preventive effects of statin use against PSD may be mediated by its interactions with IL-6.

1. Introduction

Post-stroke depression (PSD) is a common and detrimental complication that is associated with poor functional recovery and increased mortality. Studies of the biological mechanisms underlying PSD have supported the formation of an inflammatory hypothesis, which proposes that increased levels of proinflammatory cytokines resulting from the ischemic brain region contribute to the etiology of PSD (Spalletta et al., 2006). A recent human study that investigated cytokine changes 1 year after stroke found a significant increase in cytokines, such as interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, as well as the ratios of IL-6/IL-10 and TNF-α/IL-10 (Su et al., 2012). These findings strongly suggest that an immune imbalance leads to changes in cytokine levels and possibly plays a role in the pathophysiology of PSD.

Similarly, increases in specific cytokines during the acute phase of stroke have been shown to play an important role in the onset of depression. For example, increases in IL-6 levels are associated with PSD in a cross-sectional study (Spalletta et al., 2013) and increases in IL-18 levels with PSD at 6–18 months in a longitudinal study (Yang et al., 2010). However, the relationship between changes in cytokines and PSD has not been consistently observed due to differences in study design, the studied time phase of stroke, and the use of small sample sizes. Furthermore, statins (3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors), which are widely prescribed for the primary and secondary prevention of stroke due to their lipid-lowering functions, are thought to have anti-inflammatory effects that are protective against depression (Stafford and Berk, 2011; Parsaik et al., 2014). However, the anti-inflammatory properties of statins have yet to be considered in the pathophysiology of PSD.

Therefore, the present study aimed to determine whether IL-6 and IL-18, measured shortly after stroke, were associated with

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depression at baseline and at a 1-year follow-up examination after stroke, using data from a longitudinal post-stroke cohort. Additionally, this study aimed to examine the interaction between statin use and cytokine levels on the risk of depression after stroke. IL-6 and IL-18 were chosen for investigation because they are associated with the induction of acute and delayed neuro-inflammation, respectively (Felderhoff-Mueser et al., 2005). Moreover, IL-6 and IL-18 are associated with negative functional outcomes and depression following stroke (Spalletta et al., 2013; Yang et al., 2010; Zaremba and Losy, 2003).

2. Methods

2.1. Study overview

The present analysis was conducted as a part of a larger study, which was previously published (Kim et al., 2012), that used a naturalistic prospective design to investigate psychiatric disorders in stroke survivors. Participants were consecutively recruited from among all patients who were hospitalized within the Department of Neurology at Chonnam National University Hospital in Gwangju, South Korea for a recent ischemic stroke. Among recent ischemic stroke patients diagnosed by imaging studies, those with life-threatening physical illness, communication difficulties, comorbid neuro-psychiatric comorbidities, including dementia, Parkinson's disease, brain tumor, epilepsy, psychoses and substance-dependence, and with a Mini-Mental state examination score (Folstein et al., 1975) <16 were excluded. Post-stroke assessments were carried out within 2 weeks and at 1 year after stroke to estimate the consequences of stroke during both the acute and chronic states. Written informed consent was obtained from all participants and the study was approved by the Chonnam National University Hospital Institutional Review Board.

2.2. Depression diagnosis and covariates

At both baseline and the 1-year follow-up examination, diagnoses of depressive disorders were determined using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1988), a structured diagnostic psychiatric interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Any PSD was defined as a combination of major and minor depressive disorders. The following demographic and clinical covariates, which are potentially associated with PSD or cytokines (Kutlubaev and Hackett, 2014; Yudkin et al., 2001), were included as covariates in this analysis: age, gender, years of education, living alone, antidepressant use, previous history of depression and stroke, stroke severity using the criteria of the National Institute of Health Stroke Scale (NIHSS; Kasner et al., 1999), stroke localization by hemisphere (left, right, or bilateral) and location (anterior, posterior, or both), body mass index, smoking, vascular risk factors (including hypertension, diabetes, heart disease) and cholesterol level (including high- and low-density lipoprotein, triglycerides and total cholesterol).

2.3. Statin use

Research neurologists managed the patients based on guidelines for the management of stroke (Sacco et al., 2006). All prescribed drugs and self-medication were recorded, including statins (atorvastatin, fluvasatin, lovastatin, mevastatin, pravastatin and rosuvastatin). Statin use was examined both at baseline and follow-up. Further adjustment of statin use was conducted during the follow-up, taking into account the effect of statin use over the previous year.

2.4. Estimation of cytokine levels

Cytokine levels were measured at baseline but not at follow-up. Fasting venous blood was obtained within 2 weeks after stroke. The serum levels of IL-6 and IL-18 were measured using solid phase sandwich enzyme-linked immunosorbent assay (ELISA) kits (Invitrogen, Camarillo, CA, USA) according to the manufacturer's specifications. To minimize assay variance, all samples were analyzed on the same day, in duplicate in a random order, by a technician blind to the clinical diagnoses. The lower detection limits were 1.61 pg/mL for IL-6 and 103.28 pg/mL for IL-18. The intra-assay coefficients were <7%.

2.5. Statistical analysis

Exposure variables were IL-6, IL-8, and statin use at baseline. Outcome variables were PSD status, both at baseline and at follow-up. Covariates included sociodemographic and clinical characteristics at baseline. The sociodemographic and clinical characteristics were compared between any PSD and no PSD groups at baseline, using *t*-tests or chi-square (χ^2) tests as appropriate. The IL-6 and IL-18 levels and statin use evaluated at baseline were compared among PSD statuses at both examination time-points using *t*-tests and χ^2 tests, accordingly. The individual effects of IL-6, IL-18 and statin use on PSD outcomes were assessed using multivariate logistic regression models after adjustment for the baseline characteristics found to be associated with PSD ($p < 0.1$). The interactions between cytokine levels and statin use were tested using the same regression models. Since antidepressant use is associated with cytokine levels (Taraz et al., 2013), additional sensitivity analyses were conducted with the same analytical method after excluding participants taking antidepressants. All statistical analyses were carried out using SPSS 21.0 software [Chicago, IL, USA].

3. Results

Of the 423 patients who consented to participate in the study, 286 (68%) agreed to submit to blood collection and formed the baseline sample. Of these 286 patients, 222 (78%) were followed-up at 1 year after stroke. Any PSD was diagnosed in 80 patients (28%) at baseline and 53 patients (24%) at 1 year. Those with any PSD were older, and were more likely to have a prior history of depression and stroke, a more severe stroke, as measured by the NIHSS, and an anterior stroke location ($p < 0.1$). These factors were considered to be covariates in later analyses. Although, covariates associated with cytokine levels were also included in the analyses to account for the factors that link cytokines and PSD, no significant factor effects were found.

The levels of IL-6 and IL-18 and statin use were compared according to the presence of PSD at both examination time-points (Table 1). Any PSD at both examination time-points was associated with higher IL-6 and IL-18 levels, although the association between IL-18 and PSD at the 1-year follow-up had borderline significance. The individual effects of IL-6 and IL-18 on PSD at both examination time-points were significant after adjustment for the covariates. Meanwhile, statin use was only significantly associated with PSD at 1 year and a similar effect of statin on PSD was found after adjustment.

The associations between IL-6 and IL-18 and PSD at both examination time-points according to statin use are delineated in Fig. 1. Significant associations between the levels of both cytokines and PSD were prominent in patients who did not use a statin. However, in the statin use group, only the level of IL-6, which is associated with the acute inflammatory response (Spalletta et al., 2013), had a significant effect on baseline PSD after adjustment. At 1 year, there