Psychoneuroendocrinology 90 (2018) 85–91

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Changes in pro-inflammatory cytokine levels and late-life depression: A two year population based longitudinal study

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ARTICLE INFO

Keywords:
Depression
Geriatric psychiatry
Inflammation
Cytokines
Longitudinal studies

ABSTRACT

Longitudinal associations of cytokine levels with depression are unclear. This study aimed to investigate cross-sectional and prospective associations between five serum pro-inflammatory cytokine levels and late-life depression. 732 Korean people aged 65+ were evaluated at baseline. Of 631 without depression (Geriatric Mental State schedule) at baseline, 521 (83%) were followed over a 2 year period and incident depression was ascertained. Serum tumor necrosis factor-α, interleukin (IL)-1α, IL-1β, IL-6, and IL-8 levels were assayed at both baseline and follow-up. Associations between cytokine levels and depressive status were evaluated using linear regression models, considering potential covariates (demographics, cognitive function, disability, lifestyle factors, and vascular risk factors) and applying Bonferroni corrections. Prevalent depression at baseline was significantly associated with higher contemporaneous levels of IL-1β and IL-8, independent of relevant covariates and after applying Bonferroni corrections. In the analyses of the five cytokine levels in combination, independent associations were found between prevalent depression and increased numbers of cytokines at higher levels at baseline. Incident depression was significantly associated with increases in IL-1β, IL-6, and IL-8 levels during the follow-up independent of relevant covariates and after applying Bonferroni corrections. In combination analyses, incident depression was independently associated with higher numbers of cytokines showing increasing levels over the same follow-up period. However, incident depression was not predicted by higher baseline pro-inflammatory cytokine levels in any analysis. Our findings suggest that depression might affect serum cytokines alterations and lead to inflammatory processes in late-life.

1. Introduction

Late-life depression is common and is associated with a substantial disease burden (Kok and Reynolds, 2017). With increasing life spans globally, the prevalence and morbidity of depression are expected to increase considerably (Kok and Reynolds, 2017). Understanding the etiology of depression in late life is an important step toward early detection and effective treatment. Late-life depression has complex and heterogeneous etiologies, including hypothalamic-pituitary-adrenal (HPA) axis dysfunction, vascular risk factors, and deficits in neurotransmitter signaling (Taylor et al., 2013). In addition, inflammatory processes have also been received attention (Leonard and Maes, 2012).

Cytokines are believed to play a pivotal role in the regulation of the inflammatory response. The involvement of pro-inflammatory cytokines (e.g., tumor necrosis factor alpha (TNF)-α, interleukin (IL)-1, IL-6, IL-8) in depression pathogenesis has been supported by animal and human studies (Dantzer et al., 2008; Maes, 2011). In animals, administration of pro-inflammatory cytokines has been found to induce depressive behavior (Dantzer, 2001), and some antidepressants have been suggested to have a cytokine-linked anti-inflammatory effect (Rana et al., 2016). In adult humans, a recent meta-analysis of 82 case-control studies reported that peripheral levels of cytokines including TNF-α and IL-6 were elevated in patients with major depressive disorder compared to healthy controls (Köhler et al., 2017). Similar findings have been reported for late-life depression from cross-sectional designs, including increased serum TNF-α and IL-6 associated with depression (Bremmer et al., 2008; Penninx et al., 2003; Tiemeier et al., 2003). Moreover, recent studies using [11C] PK11195 positron emission tomography, which can measure inflammation in the brain directly, suggested associations between neuroinflammation and depression both in adult and late-life (Su et al., 2016; Holmes et al., 2017). However, causal relationships cannot be concluded from case-control and cross-sectional

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https://doi.org/10.1016/j.psyneuen.2018.02.006
Received 14 September 2017; Received in revised form 7 February 2018; Accepted 9 February 2018

investigations, since altered cytokine levels may also be secondary to depression-related dysfunction (Kop and Gottdiener, 2005). Longitudinal studies maybe more appropriate for clarification, although these have been scarce and have reported inconsistent findings. The Sydney Memory and Aging study reported that two year incident depressive symptoms evaluated using the Geriatric Depression Scale (GDS) (Yesavage et al., 1982) were associated with IL-8 at baseline in elderly participants aged 70–90 years (Baune et al., 2012). The In-CHIANTI (Invecchiare in Chianti, aging in the Chianti area) study reported that persons aged 65 or over with high IL-1 receptor antagonist level at baseline had a higher risk of developing depressive symptoms, evaluated using the Center for Epidemiological Studies–Depression Scale (Radloff, 1977) over a six year follow-up (Milaneschi et al., 2009). In both studies, incident depressive symptoms were not predicted by other serum cytokines including TNF-α and IL-6. Another longitudinal study in Italian residents aged 65 or over did not find any association between blood inflammatory proteins, including TNF-α or IL-6, and the 4-year risk of incident depressive symptoms evaluated using the GDS (Forti et al., 2010). Furthermore, the opposite direction of association has been reported, in that depressive symptoms evaluated using the Beck Depression Inventory-II (Beck et al., 1996) at baseline predicted changes in IL-6 levels, while baseline IL-6 levels did not predict depressive symptom changes in a six year longitudinal community study of healthy elders (Stewart et al., 2009). Summing up, the directionality of the inflammation and depression association has yet to be determined.

These discrepancies in previous findings might be due to the method employed for evaluating depression, in that heterogeneous assessment scales were used and case status defined on the basis of a cutoff score rather than a structured interview. In addition, most studies assayed blood cytokine levels only at baseline, which is unlikely to determine the causal relationships. To address this, we analysed data from a two-year longitudinal study to investigate both cross-sectional and prospective associations of serum cytokine levels measured both at baseline and follow-up with depression in late-life, diagnosed by a widely used structured diagnostic interview.

2. Method

A secondary analysis was carried out on data from a community based prospective survey of late-life psychiatric morbidity carried out in Kwangju, South Korea from 2001 to 2003. All participants gave written formal informed consent at each examination. This study was approved by the Chonnam National University Hospital Institutional Review Board.

2.1. The baseline sample and measurements

A cross-sectional survey of a geographically defined population was carried out in 2001. The sampling procedure and measurements have been described previously (Kang et al., 2015). In brief, 732 community residents aged 65 or over within two defined geographic catchments of Kwangju, South Korea were recruited from national residents registration lists (5% refusal rate). Examinations included a fully structured diagnostic interview for depression; blood samples taken for five serum pro-inflammatory cytokines; and formal assessment of potential confounding factors.

2.1.1. Depression

Depression was assessed using the community version of the Geriatric Mental State schedule (GMS) (Copeland et al., 1986). The items for this instrument were derived mainly from DSM or ICD criteria with some modification for old age. The GMS is a fully structured diagnostic interview for mental disorders and focuses on the one month preceding the interview. It has been widely used in international epidemiological research for depression in late-life (Copeland et al., 1991), including research across European sites (Copeland et al., 1999), specific application and validation in East Asian communities (Kuh, 1992; Chong et al., 2001; Chen et al., 2004), and incorporation as the principal measure of affective disorder in the 10/66 research programme in Latin America, China and India (Llibre Rodriguez et al., 2008): the largest community study to date of mental health in older people. It takes approximately 30–40 min to administer by specifically trained interviewers. Diagnosis of depression in the last month is conventionally generated using the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) algorithm on a 0–5 scale. Participants rated as AGECAT 3, 4, and 5 are considered to be likely cases, those rated as 1 and 2 are considered to be sub-cases, and those rated as 0 to have no relevant symptomatology. With typical community prevalence estimates between 10 and 20%, the GMS-AGECAT depression criterion encompasses both moderate and severe symptomatology, and therefore a broader syndrome than DSM-IV major depression. Satisfactory agreement with Hamilton and Montgomery Asberg Depression scale cut-offs have also been demonstrated (Mottram et al., 2000). The GMS was translated into Korean according to a formal standardization process (Kim et al., 2003). As in other studies (Chen et al., 2004; Copeland et al., 1999; Llibre Rodriguez et al., 2008), a 'stage one' (non-hierarchical) confidence level of 3 or above from the AGECAT algorithm was used to define depression.

2.1.2. Blood samples and biochemical analyses

Participants were instructed to be fasting, and blood samples were carried out in the morning and were collected in a fasting state in 93% of participants. Venous blood samples were collected in tubes with no additives, and were centrifuged to isolate serum. Serum aliquots were stored at −70 °C within 2 h of collection until analyses were performed. Biochemical assays were carried out for five serum pro-inflammatory cytokines: TNF-α, IL-1α, IL-1β, IL-6, and IL-8. Serum cytokine levels were measured using a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) kit (Invitrogen, Camarillo, CA, USA) according to the manufacturer's specifications. The intra-assay coefficients of variation were 3 ~ 6% for TNF-α, 4 ~ 6% for IL-1α, 4 ~ 7% for IL-1β, 4 ~ 5% for IL-6, and 2 ~ 4% for IL-8. The inter-assay coefficients of variation were 5 ~ 7% for TNF-α, 4 ~ 8% for IL-1α, 5 ~ 9% for IL-1β, 6 ~ 9% for IL-6, and 3 ~ 6% for IL-8.

2.1.3. Covariates

Factors associated with serum cytokine levels, and potentially confounding associations of interest, were investigated considering previous research findings (Baune et al., 2012; Milaneschi et al., 2009; Forti et al., 2010; Stewart et al., 2009). Age, gender, and education were recorded. Cognitive function was evaluated by the Korean version of the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Disability was assessed by the Korean version of the World Health Organization Disability Assessment Schedule II (WHODAS II) (Kim et al., 2005). Smoking history and current smoking status were ascertained. A lifetime history of alcohol consumption was obtained from the participants, and corroboration from family members was sought. Problem drinkers were defined on the basis of consumption over the previous three months of greater than 14 drinks per week for men or greater than 7 drinks per week for women, according to guidelines from the National Institute of Alcohol Abuse and Alcoholism (NIAAA, 1995). Self-rated physical activity was measured by asking about work and leisure activity over the previous month on the basis of a4-point scale (very active, fairly active, not very active, not at all active), and low physical activity was defined in case of not very active or not at all active as a binary variable according to the standard protocol adopted by the 10/66 Dementia Research Group (Prince et al., 2003). For vascular risk factors and disorders, self-reported disorders (stroke, heart disease, hypertension, diabetes), measured obesity (body mass index > 25 kg/m^2) and hypercholesterolemia (fasting cholesterol > 200 mg/dl) were evaluated. The presence or absence of any vascular risks was used in the