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Lower CSF interleukin-6 predicts future depression in a population-based sample of older women followed for 17 years

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ABSTRACT

Objective: The literature regarding cerebrospinal fluid (CSF) cytokines in geriatric depression is sparse. The aim of this study was to examine associations between CSF interleukin-6 (IL-6) and related proinflammatory cytokines and current and future depression in a population-based sample of older women who were followed for 17 years.
Methods: 83 non-demented women aged 70–84 years who participated in the Prospective Population Study of Women in Gothenburg, Sweden took part in a lumbar puncture in 1992–3. CSF- IL-6, interleukin-1β (IL-1β), interleukin- 8 (IL-8) and tumor necrosis factor-α (TNF-α) were measured. Psychiatric symptoms were rated with the Comprehensive Psychopathological Rating Scale at baseline and at three subsequent face-to-face examinations. Depression (major or minor) was diagnosed in accordance with DSM-IV/DSM-IV research criteria.
Results: At baseline, women with ongoing depression had lower levels of IL-6 ($p < 0.04$), IL-8 ($p < 0.05$) and TNF-α ($p < 0.05$) compared with those without depression. In women without depression at baseline, lower CSF IL-6 levels predicted depression at one or more follow-up examination ($p < 0.03$). Results from the generalized linear mixed logistic model using all baseline and follow-up data on depression status and Mini Mental State Examination score showed a significant relationship between IL-6 and depression ($p = 0.005$ OR 0.370 CI [0.184–0.744]).
Conclusion: Lower levels of CSF IL-6 were associated with current depression and with future depression during a follow-up of almost two decades. Our findings suggest that lower levels of CSF IL-6 may be related to depression vulnerability in later life.

1. Introduction

In recent years it has been hypothesized that changes in the immune system might play an important role in pathophysiological processes related to depression (O'Brien et al., 2004; Mossner et al., 2007; Miller et al., 2009; Schrepf et al., 2012). Proinflammatory cytokines may activate the hypothalamic–pituitary–adrenal (HPA) axis, (Leonard, 2000; O'Brien et al., 2004) modulating monoamines in the CNS and leading to depressive symptoms (Chaouloff, 2000). Cytokine receptors have been localized in the hippocampus and hypothalamus, with the highest density observed for interleukin-6 (IL-6) receptors (Hopkins and Rothwell, 1995). Clinical studies have shown that serum levels of proinflammatory cytokines are disturbed in patients with depression. A recent meta-analysis demonstrated that, while individual studies showed both positive and negative results, levels of plasma tumor necrosis factor-α (TNF-α) and plasma IL-6 were significantly higher in persons with major depression than those who were not depressed (Dowlati et al., 2010).

Despite abundant evidence of peripheral immune alterations in persons who are depressed, there are to date few published studies on cytokine levels in the cerebrospinal fluid (CSF) of depressed persons. To further clarify the roles of cytokines in depression, CSF central measurements are needed. Existing CSF studies are cross-sectional and based on relatively small clinical samples. Two studies (one of which focused on geriatric depression) showed *lower* CSF IL-6 levels in depressed patients compared to mentally healthy controls (Levine et al., 1999; Stubner et al., 1999). Another reported higher levels (Lindqvist et al., 2009), and two further studies

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showed no differences between groups (Carpenter et al., 2004; Martinez et al., 2011). Regarding other cytokines, higher CSF IL-1β (Levine et al., 1999) levels distinguished acutely depressed inpatients from healthy controls, whereas levels of TNF-α (Levine et al., 1999), IL-8, TNF-α and IL-1β levels did not differ between the groups (Lindqvist et al., 2009). Clinical studies may miss depressed persons in the population due to referral bias. The need for epidemiological approaches has been stressed (Dantzer, 2012). To our knowledge there are to date no studies examining CSF proinflammatory cytokines and depression in population-based samples. We have previously reported cross-sectional CSF findings from a population-based sample of women in support of both neurodegenerative and vascular etiology for depression in late life (Gudmundsson et al., 2007). The aim of the present study was to examine a possible association with proinflammatory cytokines in the same cohort. As most studies of peripheral plasma levels have shown that elevated cytokine levels were associated with depression, we hypothesized that we would find similar associations in CSF. As prospective studies may provide insights into pathological mechanisms that cross-sectional studies cannot, a second aim was to determine whether these cytokines were associated with *future* depression in older women followed over a period of 17 years.

2. Methods

2.1. Subjects

The study sample was derived from the Prospective Population Study of Women (PPSW), a population-based survey in Gothenburg, Sweden (Bengtsson et al., 1973). The sample was obtained from the Swedish population register, based on birth date, and included both those living in private households and in residential care. The original sample has been described in detail previously (Bengtsson et al., 1973; Gudmundsson et al., 2007). Briefly, the study began in 1968–1969 and included a representative sample of 1462 women living in Gothenburg, Sweden born on certain dates in 1908, 1914, 1918 and 1922.

In 1992–1993, 837 surviving women were invited to participate in a psychiatric examination, which for the purpose of the current study will be referred to as the baseline examination. Among 590 who agreed to take part, 85 (aged 70–84 years) consented to undergo a lumbar puncture (LP). Two of these women who were diagnosed with dementia at the time of the LP were excluded from the current analyses, leaving 83 women born in 1908 ($n = 2$), 1914 ($n = 6$), 1918 ($n = 33$) and 1922 ($n = 42$). The mean age of the participants at baseline in 1992–1993 was 72.5 years (SD 3.1).

Follow-up psychiatric examinations were conducted in 2000, 2005 and 2009. In 2000, 61 out of 70 surviving women accepted participation (response rate 87%). In 2005, 41 out of 49 surviving women agreed to be examined (response rate 84%). In 2009, 19 of the 25 surviving women took part (response rate 76%).

After complete description of the study, written informed consent was obtained from all participants at each examination wave. For women with dementia at follow-up, close informants gave proxy consent. The study was approved by the Ethics committee for medical research at the university of Gothenburg.

As previously reported (Gudmundsson et al., 2007), there were no differences at baseline between the women who participated in the lumbar puncture ($n = 85$) and those who participated in the psychiatric exam only ($n = 505$) with regard to age, psychiatric illnesses, including symptoms of depression, smoking status, alcohol intake, physical activity, systolic and diastolic blood pressures, body mass index, blood levels of cholesterol, high density lipoprotein, and triglycerides, age of menopause, history of angina pectoris, myocardial infarction and diabetes, and use of a variety of medications including lipid-lowering agents, antihypertensive agents and hormone replacement therapy. Further, no differences could be shown regarding Mini Mental State Examination (MMSE) scores (Folstein, Folstein et al., 1975) ($p = 0.438$), and ratings of the personality traits neuroticism ($p = 0.666$) and extroversion ($p = 0.941$) as measured by the Eysenck Personality Inventory.

2.2. Procedures

The clinical examination was conducted at a geriatric outpatient department or in the participant's home and included comprehensive social, functional, physical, neuropsychiatric and neuropsychological examinations, as well as a close informant interview (Palsson et al., 2001). Information about medication use was collected and classified according to the Anatomical Therapeutic Chemical Classification codes (ATC) (Oslo, 1997).

2.3. Psychiatric examination and diagnostics

The baseline psychiatric examination was semi-structured and performed by psychiatrists in 1992–1993. Follow-up exams were carried out by trained psychiatric nurses. The Comprehensive Psychological Rating Scale (CPRS) (Asberg et al., 1978) was used to rate psychiatric symptoms at baseline and each following exam. Major depression was diagnosed in accordance with DSM-IV and minor depression was diagnosed according to DSM- IV research criteria (either a sad or depressed mood or loss of interest or pleasure in nearly all activities). In total at least 2 but less than 5 additional symptoms (American Psychiatric Association, 1994). Depression symptom burden was measured with the Montgomery-Åsberg Depression Rating scale (MADRS), which is derived from the CPRS (10 items, maximum score 60) (Montgomery and Asberg, 1979).

The neuropsychiatric exam has been described in detail (Skoog et al., 1993). Briefly, the exam included the MMSE and tests of short- and long term memory as well as tests of aphasia, apraxia, agnosia and abstract thinking. The diagnosis of dementia was made on the basis of the neuropsychological examination and the interview with the close informant, with each considered separately, using DSM-III-R criteria (Association 1987). Each symptom had to have attained a level at which it caused the subject substantial difficulty in social functioning and the duration of dementia had to be at least six months. A final diagnosis was made on the basis of the combined information (Skoog et al., 1993). Dementia was an exclusion criterion at baseline.

2.4. CSF analyses

Lumbar punctures were carried out in 1992–1993 only. CSF-samples (12 ml) were taken through the L3/L4 interspace and gently mixed to avoid gradient effects. The samples were immediately centrifuged at 2000*g* for 10 min to eliminate cells and other insoluble materials, aliquoted in 1 ml portions, snap frozen at −80 °C, stored at that temperature and brought in an unbroken freeze chain to the laboratory for analyses. CSF levels of IL-1β, IL-6, IL-8, and TNF-α were analyzed by certified laboratory technicians using the Human Pro-inflammatory II 4-Plex Assay Ultra-Sensitive Kit (Meso Scale Discovery, Gaithersburg, MD, USA). Intra-assay coefficients of variation were below 10% for all analytes. The limit of detection was 0.61 pg/ml. Cytokine concentrations below the detection limit were set to 0.6 pg/ml.

2.5. Statistical analysis

Differences in cytokine levels were tested with the non-parametric Mann–Whitney-U test. Binary logistic regressions were