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The association between depressive symptoms, cognitive function, and inflammation in major depression

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ABSTRACT

The purpose of this study was to assess the association between IL-6 and CRP with depressive items and cognitive function. We included 112 outpatients with major depression from an exercise trial and 57 healthy controls. IL-6, high sensitive CRP (hsCRP), and cognitive function were assessed in all subjects. After baseline assessment, patients were randomised to either a 3 months exercise intervention or an exercise control group. Post-intervention IL-6, hsCRP, depressive symptoms, and cognitive function were reassessed in the patient group. IL-6 and hsCRP were significantly increased in depressed patients compared to healthy controls ($p = 0.02$ and 0.04). These differences were no longer significant after adjustment for lifestyle associated variables. We found no association between immune markers and specific depressive symptoms at baseline or as change over time. Regarding the cognitive tests, IL-6 was positively associated with Serial sevens ($p = 0.008$) and hsCRP was inversely associated with Trail making A ($p = 0.02$) and design fluency ($p = 0.001$) at baseline. At 3 months follow-up IL-6 and hsCRP levels did not significantly change from baseline and did not differ between the two patient groups. Depression scores was lower compared to baseline but did not differ between groups. Combining the two groups, a decrease in IL-6 was associated to decreased verbal fluency ($p = 0.02$), and a decrease in hsCRP was associated with improvement in Trail making A ($p = 0.005$). In conclusion, the level of IL-6 and hsCRP was increased in depressed outpatients but was not associated to specific depressive symptoms. In terms of cognitive function, we found that higher hsCRP levels were associated to lower psychomotor speed both at baseline and at follow-up.

1. Introduction

Several conditions such as cardiovascular disease (Celano and Huffman, 2011), type 2 diabetes (Alexandraki et al., 2006; Ali et al., 2006) and obesity (Capuron et al., 2011) are characterised by a high prevalence of depression and chronic low-grade inflammation. While some studies finds an increased immune activation in depressed patients (Howren et al., 2009), results from studies adjusting for factors such as body mass index, physical fitness and the use of antidepressants are less convincing (Vogelzangs et al., 2012).

Peripheral inflammatory activation potentially activates the immune system within the blood–brain barrier by direct or indirect pathways (Dantzer et al., 2008a). Furthermore, animal experiments have shown that systemic administration of lipopolysaccharide or pro-inflammatory cytokines can induce central expression of pro-inflammatory cytokines in the brain, which induced sickness behaviour in a time- and dose-dependent manner (Laye et al., 1994; Quan et al., 1999). This has given rise to a theory implying a possible role for cytokines and other immune components in depression, either as a cause or as an epiphenomena (Schiepers et al., 2005).

Symptoms experienced during an infection such as fatigue, sleep disturbances, anorexia and anhedonia shares similarity to the neurovegetative symptoms experienced during a depressive episode. A study of patients with interferon-α (IFN-α) induced depression and medically healthy depressed patients, found that the cytokine induced depression had greater symptoms of psychomotor retardation and weight loss but lower symptoms of feelings of guilt compared to the medically healthy depressed patients (Capuron et al., 2009). This supports findings from recent studies suggesting that immune activation primarily affects vegetative symptoms such as appetite loss, insomnia, and fatigue rather than

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affective symptoms such as depressed mood and feeling of guilt (Duivis et al., 2013; Inagaki et al., 2013).

The association between cognitive function and inflammatory markers have been studied in various disease entities. For example, CRP levels have been found to predict dementia (Kuo et al., 2005), and CRP is associated to impairment of several cognitive domains in patients with peripheral arterial disease (Mangiafico et al., 2006). Despite indications of cognitive impairment in patients with depression (Ravnkilde et al., 2002), studies investigating the association between immune markers and cognitive function in depression are limited. However, high IL-6 and CRP levels has been associated with impairment of psychomotor speed (Chang et al., 2012) and verbal memory in subjects with clinical depression (Grassi-Oliveira et al., 2011).

Whether the variance in immune markers correlates to the variance in individual depressive symptoms has not previously been explored in depressed patients. Neither has the impact of inflammation on symptoms of depression and cognitive function been investigated in depressed subjects compared to healthy controls. The objective of this study was to explore possible associations between IL-6, hsCRP, individual depressive symptoms and cognitive function. Also, to investigate if any association between IL-6, hsCRP and depressive symptoms and cognitive function was different in depressed subjects compared to healthy controls. Lastly, estimating longitudinal associations between changes in inflammatory markers and changes in depressive symptoms and cognitive function would test the strength of any association found at baseline.

2. Methods

2.1. Study population

All patients were recruited for participation in the DEMO-II trial ($n = 115$), a randomized clinical trial evaluating the antidepressant effect of aerobic exercise (Krogh et al., 2012). Eligible participants were men and women between 18 and 60 years of age, referred from a clinical setting by a physician or a psychologist, with a diagnose of major depression (DSM-IV) based on the Danish version of the Mini International Neuropsychiatric Interview (M.I.N.I) (Bech et al., 1999). The participants all scored above 12 on the HAM-D_{17} and were able to comprehend the informed consent statement. Exclusion criteria were current drug abuse, any antidepressant medication within the last 2 months, current psychotherapeutic treatment, contraindications to physical exercise, regular recreational exercise over 1 h per week, suicidal behaviour according to the 17-item Hamilton depression rating scale (HAM-D_{17}, item 3 score >2), pregnancy, or current/previous psychotic or manic symptoms. Healthy controls were recruited through the media and group matched to the patients on sex, age, and body mass index ($n = 57$). The healthy controls were free of any current or previous psychiatric diseases assessed by the M.I.N.I (Bech et al., 1999). Of the 115 patients included in the DEMO-II trial we have IL-6 and CRP assessment from 112 patients, which constitutes the patient group for the current study. The evaluation of patients and healthy controls were commenced in parallel.

2.2. Assessment of mood and cognitive function

Depression severity was assessed using the Hamilton depression rating scale with 17-items (HAM-D_{17}) (Hamilton, 1960). Based on the HAM-D_{17} we constructed two subscales focusing on mood and neurovegetative symptoms. The mood subscale was constructed by pooling the scores from HAM-D_{17} items related to mood – i.e. items 1–3. The neurovegetative subscale was constructed by pooling scores from items in HAM-D_{17} related to sleep, fatigue, and loss of appetite – i.e. items 4–8, 12, and 13. Assessment of cognitive function included six domains. Memory was assessed by Buschke's Selective Reminding Test (Buschke and Fuld, 1974) and Rey's Complex Figure Test (Meyers et al., 1996), attention domain by the Digit Span Test (Wechscler, 1981), Serial Sevens (Smith, 1967) and Stroop's Test (Alvarez and Emory, 2006), psychomotor speed by Trail making A and B (Reitan, 1955) and the Digit Symbol Test (Wechscler, 1981), language domain by the Verbal Fluency Test (S and animals) (Borkowski et al., 1967), and executive function by the design fluency test (Baldo et al., 2001).

2.3. Physical examination

For the physical examination, the participants were requested to meet at the research department between 8:00 and 10:00 a.m. The participants were instructed not to take any food or liquids except for water beginning from midnight prior to the examination and abstain from strenuous physical activity prior to the examination. Height and weight was measured using an electronic weight (Sohnle Medical®, Type 7700, Backnang, Germany) waist circumference was assessed by standardized procedures and reported as the mean of two measurements. Blood pressure was obtained after 5 min rest with the participant in a sitting position using a certified digital blood pressure monitor (Omron M6, Omron Healthcare Co. Ltd, Kyoto, Japan). The average of three measurements at the right arm is reported. An indwelling venous catheter was inserted in the antecubital vein and blood samples collected in tubes containing ethylenediamine tetra acetic acid (EDTA) after 5 min rest in a sitting position. A bicycle cardiopulmonary exercise test based on L.B. Andersen's cycle exercise protocol (Andersen, 1995) was used to estimate the participants cardiovascular fitness. The test bike was an Ergomedic 893e from Monark, Vansbro, Sweden.

The plasma samples were stored in aliquots at −80 °C. Plasma concentrations were measured blinded for case and controls status. hsCRP measurement was performed using the Immulite 2000 (Siemens). The IL-6 plasma concentration was assessed using the Human IL-6 High Sensitivity ELISA kit (eBioscience, Bender MedSystems GmbH, Vienna, Austria). The same batch numbers was used for the entire experiment. The intra-assay coefficient of variance for the preset study varies from 7.3% to 10.2%, which is within the intra-assay variance of 0.3–15.9% specified by the manufacturer.

2.4. Longitudinal assessment

After baseline assessment the participants were randomized to 3 months supervised aerobic training or an attention control group doing low impact exercise. This has been described in detail elsewhere (Krogh et al., 2012). Despite a significant increase in maximal oxygen uptake in the aerobic exercise group there was no difference on depression scores, IL-6, or hsCRP levels post-intervention. Visual memory, evaluated as the recall function on the Rey complex figure test was the only cognitive function that post-intervention was superior in the exercise group compared to the control group. Exercise had no effect on any other cognitive function. Since we found no effect of the aerobic training on inflammatory markers and only partial effect on cognitive function, we combined both intervention arms and treated them as a cohort for this report.

2.5. Statistics

Differences between depressed patients and healthy controls were evaluated using Chi-square test and independent-samples *t*-test. The inflammatory markers were log transformed prior to analyses. The association between immune markers and depres-