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Soluble cell adhesion molecules in late-life depression

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ABSTRACT

Background: Late-life depression has been associated with vascular diseases and with increases in circulating cytokines and cell adhesion molecules in the prefrontal cortex. We hypothesized that soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) would be increased in late-life major depression.

Methods: Serum levels of sICAM-1 and sVCAM-1 were measured in subjects over 60 with major depression (N = 23), subsyndromal depression (N = 20) and controls (N = 25). Depression severity was assessed using the Montgomery-Åsberg (MDRS) and Geriatric Depression (GDS) rating scales.

Results: There was no significant increase in sICAM-1 ($p = 0.240$) or sVCAM-1 ($p = 0.600$) in depression nor was there any correlation of either molecule with depression severity. Adjusting for differences in cognitive impairment did not alter these findings. There was also no difference between subjects with an early onset of depression (before 60) and those with late-onset depression.

Conclusions: These findings do not provide evidence that previously reported increases in serum cytokines in depression are due to peripheral vascular disease. Although we assessed subjects for vascular diseases it is possible that subtle but important differences between groups may still have been present and may have contributed to our negative findings.

Our results suggest central nervous system mechanisms, such as related to HPA axis activation, may be responsible for the enhanced inflammatory response in depression.

Key words: major depression, inflammation, vascular disease, cytokines

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Introduction

Depression is a common and debilitating condition, which is strongly associated with stroke and coronary artery disease (Thomas *et al.*, 2004). These diseases involve an inflammatory response (Ross, 1993), including increases in serum soluble cell adhesion molecules (Ridker *et al.*, 1998) and cytokines (Ridker *et al.*, 2000). Cell adhesion molecules (CAMs) are expressed on the vascular endothelium in response to cytokine stimulation and most CAMs are released as soluble isoforms from the endothelium and circulate in the blood in these soluble forms. Reports show that sICAM-1 and sVCAM-1 levels are elevated after cerebral infarction and in subjects with vascular risk factors (Fassbender *et al.*, 1999).

We have previously reported an increase in intercellular adhesion molecule-1 (ICAM-1) (Thomas *et al.*, 2000) and vascular cell adhesion molecule-1 (VCAM-1) (Thomas *et al.*, 2002) on the cerebral endothelium in the dorsolateral prefrontal cortex in post mortem studies in late-life depression and an increase in interleukin-1B in blood in elderly subjects with major depression (Thomas *et al.*, 2005). We hypothesized that serum levels of soluble ICAM-1 (sICAM-1) and VCAM-1 (sVCAM-1) would be increased in late-life depression and that these increases would correlate with the severity of the depression.

Method

To test these hypotheses we recruited three groups of subjects, all of whom were over 60 years old: (1) a major depression group who had DSM-IV major depression (American Psychiatric Association, 1994) and scored $\geq$20 on the Montgomery-Åsberg Depression Rating Scale (MDRS) (Montgomery and Åsberg, 1979); (2) a subsyndromal depression group who had had at least one previous episode of DSM-IV major depression and who had partially recovered, scoring between 8 and 19 on the MDRS; and (3) similarly aged comparison subjects who had never had any psychiatric or neurological illness and scored $<$8 on the MDRS. All subjects gave informed consent to participate in the study and those in the first two groups were recruited from our Newcastle Depression Register or from day unit and inpatient psychiatry facilities in Newcastle-upon-Tyne and Gateshead, U.K. Comparison subjects were recruited from friends and spouses of depressed subjects. None of the study subjects had any clinical evidence of dementia and all were assessed for neurocognitive impairment using both the Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975) and the cognitive component of the Cambridge Cognitive Examination (CAMCOG) (Roth *et al.*, 1999). Subjects scoring less than the standard cut-offs for global cognitive impairment (24 and 80 respectively) were excluded from entry to the study.

Subjects were given a thorough psychiatric assessment by a senior psychiatrist to determine diagnosis and a semi-structured interview by a research nurse to gather demographic and clinical data. These data were reviewed by a senior research psychiatrist (AT or JO'B). Subjects were excluded if: they had had a stroke or transient ischaemic attack; a recent (within 6 weeks) myocardial

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infarction or had unstable angina; uncontrolled hypertension; or had any current infection. From the clinical history and physical examination we obtained information about any previous coronary heart disease, hypertension, current systolic and diastolic blood pressure, diabetes mellitus (and current glucose), smoking and cholesterol level. The severity of depression was rated using both the MDRS and the 30-item Geriatric Depression Scale (GDS). Following assessment a blood sample was taken and immediately transported on ice to the laboratory where serum was aliquotted and frozen for later analysis. A second blood sample was sent for routine full blood count, biochemistry and estimation of C-reactive protein (CRP). Subjects were required to have a normal blood count and biochemistry and the upper limit for CRP was set at 18.8mg/l in accordance with previous recommendations (Wener *et al.*, 2000).

Human sICAM-1 and sVCAM-1 were measured in duplicate in serum samples using a quantitative sandwich enzyme immunoassay (kits BBE1B and BBE3, from R&D Systems Europe Ltd, Abingdon, U.K.). The assay was run in accordance with the manufacturer's instructions. Serum samples were diluted 1:20 (sICAM-1) or 1:50 (sVCAM-1) in the sample diluent provided in the kit. Plates were read at 450 nm with wavelength correction at 590 nm. Intra-assay reliability, a measure of variability within each assay, was 4.3 for sICAM-1 and 5.5 for sVCAM-1.

Group differences were examined using analysis of variance (SPSS version 10.0, Chicago) followed by unpaired t-tests as needed. Pearson's correlation coefficients were calculated to examine the relationship of depression severity to sICAM-1 and sVCAM-1 levels. To examine the effects of possible confounders, post hoc correlation coefficients, t-tests or Mann-Whitney tests were used as appropriate.

Results

Twenty-three subjects with major depression, 20 with subsyndromal depression and 25 comparison subjects met the entry criteria (Table 1). The groups did not differ in age or sex and as expected the depressed groups showed statistically significantly greater impairments in cognition. The groups did not differ in their prevalence of vascular diseases (such as hypertension or coronary heart disease) or vascular risk factors (such as smoking).

There were no differences in the serum levels of sICAM-1 or sVCAM-1 between the groups or in CRP. There were no correlations between depression severity and sICAM-1 or sVCAM-1 levels, whether measured by MDRS (sICAM-1 ($r = 0.113$, $p = 0.361$); sVCAM-1 ($r = -0.121$, $p = 0.332$)) or GDS (sICAM-1 ($r = 0.144$, $p = 0.276$); sVCAM-1 ($r = -0.151$, $p = 0.258$). There were also no correlations between sICAM-1 or sVCAM-1 levels and cognition, and therefore co-varying for cognition with either CAMCOG ($F = 0.663$, $p = 0.578$) or MMSE ($F = 0.681$, $p = 0.567$) did not affect the significance of the relationship of sICAM-1 with depression, or with sVCAM-1 and depression (CAMCOG: $F = 0.493$, $p = 0.689$; MMSE: $F = 1.668$, $p = 0.183$). Nineteen of the depressed subjects had an early onset of depression (EOD; first episode

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Table 1 Comparison of soluble cell adhesion molecule expression in late-life major depression, subsyndromal depression and healthy comparison subjects

	COMPARISON SUBJECTS N = 25	MAJOR DEPRESSION N = 23	SUBSYNDROMAL DEPRESSION N = 20	STATISTICAL COMPARISONS
Age (years)	75.6 (6.5)	75.7 (7.8)	75.0 (5.7)	$F = 0.059$ $p = 0.943$
Sex (m:f)	10:15	7:16	10:10	$\chi = 1.71$ $p = 0.425$
MMSE	28.6 (1.2)	27.0 (2.5)	26.3 (2.1)	$F = 8.039$ $p = 0.001$
CAMCOG	94.8 (4.1)	88.7 (6.7)	88.6 (6.1)	$F = 9.228$ $P < 0.001$
MDRS	1.0 (1.5)	29.3 (5.7)	12.0 (5.3)	$F = 238.594$ $P < 0.001$
GDS	3.0 (2.8)	21.0 (3.8)	15.4 (7.9)	$F = 56.801$ $P < 0.001$
CRP(mg/l)	4.1 (3.5)	5.1 (3.2)	3.8 (2.9)	$F = 0.970$ $p = 0.385$
ICAM-1 (ng/ml)	251.6 (63.2)	289.0 (106.5)	259.2 (56.3)	$F = 1.459$ $p = 0.240$
VCAM-1 (ng/ml)	578.3 (173.0)	533.2 (163.1)	580.0 (192.8)	$F = 0.514$ $p = 0.600$

MMSE = Mini-mental State Examination; CAMCOG = Cambridge Cognitive Examination; MDRS = Montgomery-Åsberg Depression Rating Scale; GDS = Geriatric Depression Scale; CRP = C-reactive protein; ICAM-1 = intercellular adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1.

before age 60) and 21 had late onset depression (LOD). The latter group was slightly older (76.9(7.1) vs 73.1(6.2)). There were no differences in sICAM-1 or sVCAM-1 level between EOD and LOD groups or between controls and LOD, before or after co-varying for age. There were also no correlations of sICAM-1 or sVCAM-1 levels with age of depression onset.

Discussion

Contrary to our hypotheses we found no evidence for significant increases in sICAM-1 or sVCAM-1 in the serum of subjects with late-life major depression and no correlation of the serum levels of these proteins with depression severity.

While it is possible the negative findings are due to inadequate numbers of subjects we think this is unlikely because similar numbers have produced robust evidence of increases in serum cytokines in previous studies and the group differences do not approach statistical significance or even suggest a consistent trend. Since age of depression onset has been most strongly associated with increased vascular disease it was possible that differences would only be apparent in LOD subjects, but we found no evidence in our sample for this. Similarly, since sCAM levels are robust markers of vascular disease it may be that differences in such diseases affected our findings. While we think this is unlikely, since the groups were very similar on all such measures, it is possible that subtle differences in vascular disease between groups may have been present and contributed to our negative results.

In our earlier report of an increase in IL-1B in late-life depression we suggested a model in which increases in sICAM-1 and sVCAM-1, and serum cytokines, would result from leakage of these isoforms from the cerebral vasculature where increases in CAMs were caused by locally produced cytokines resulting from cerebral ischaemia and inflammation (Thomas *et al.*, 2005). This was based on the vascular depression model of late-life depression, our earlier investigations, in which we reported increases in both ICAM-1 and VCAM-1 on the cerebrovascular endothelium (Thomas *et al.*, 2000; 2002) and other reports of increases in serum pro-inflammatory cytokines in late-life depression (Penninx *et al.*, 2003). The negative findings in this study do not support this model. One explanation, consistent with the vascular depression model, is that centrally produced CAMs do not pass out into peripheral blood, although there is no evidence to suggest such leakage would not occur. An alternative model involving HPA axis dysfunction is possible. In younger adults with depression a positive correlation of interleukin-1B with post dexamethasone cortisol level has been reported (Maes *et al.*, 1993) and it has been proposed that primary immune dysfunction in depression leads to elevated cytokines and HPA axis abnormalities (Penninx *et al.*, 2003), which in turn might lead to increased vascular disease in depression. However, in this model we would also expect raised peripheral CAMs but there is a paucity of studies in this area and to our knowledge none supports a relationship of HPA axis dysfunction and cytokine abnormalities in late-life depression. Further investigation to clarify the relationship of vascular disease, HPA axis changes, cytokines and late-life depression is needed.

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Conflict of interest

None.

Description of authors' roles

Dr Thomas designed the study, obtained funding, supervised patient recruitment and wrote this report. Dr Morris designed the study and supervised the laboratory and analysis and contributed to the writing of the report. Dr Davis conducted the laboratory analysis, performed the statistical analysis and contributed to the writing of the report. Dr Jackson recruited the patients for the study and carried out the clinical ratings. Dr Harrison supervised Dr Jackson and assisted in patient recruitment and contributed to the writing. Professor O'Brien designed the study, obtained funding, supervised patient recruitment and contributed to the writing of this report.

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