Brief Report

Increase in Interleukin-1β in Late-Life Depression

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Objective: Depression has been associated with increases in circulating cytokines in younger adults, and there is evidence for prefrontal inflammation in late-life depression. The authors tested the hypothesis that levels of cytokine interleukin-1β (IL-1β) would be higher in subjects with late-life major depression.

Method: Serum levels of IL-1β were measured in three groups of subjects who were older than 60: 19 subjects with major depression, 20 subjects with subsyndromal depression, and 21 healthy comparison subjects. The Montgomery-Åsberg Depression Rating Scale and the Geriatric Depression Scale were used to assess severity of depression.

Results: Compared with healthy subjects, those with major depression had significantly higher levels of IL-1β (170%); the higher levels of IL-1β strongly correlated with current depression severity. There were no significant differences between subjects with subsyndromal depression and the other two groups.

Conclusions: These findings support the existence of an inflammatory response, which may be state dependent, in late-life depression.

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There have been reports in younger adults of increases in the proinflammatory cytokine interleukin-1β (IL-1β) in major depression (1) and dysthymia (1, 2) and a report of increases in interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in late-life depression (3). One function of such cytokines is to induce expression of cell adhesion molecules on endothelial cells, and we reported an increase in intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 on the cerebral endothelium in the dorsolateral prefrontal cortex in postmortem studies in late-life depression (4). We therefore hypothesized that IL-1β would be higher in late-life depression and that this higher level would be correlated with severity of depression.

Method

We recruited three groups of subjects over 60 years old: 1) subjects who had DSM-IV-diagnosed major depression and who scored ≥20 on the Montgomery-Åsberg Depression Rating Scale (5); 2) subjects who had experienced at least one previous episode of DSM-IV major depression, who scored 8–19 on the Montgomery-Åsberg Depression Rating Scale, and who currently did not meet full criteria for major depression; and 3) comparison subjects with no current or past psychiatric illness who scored <8 on the Montgomery-Åsberg Depression Rating Scale.

All subjects gave written informed consent and were recruited from outpatient and inpatient psychiatric facilities. Comparison subjects were recruited from spouses and friends of depressed subjects. None of the study subjects had any clinical evidence of dementia, other neurological disorders, or conditions associated with inflammation such as rheumatoid arthritis, and no study subjects were taking oral steroids. Cognition was assessed with the Mini-Mental State Examination (MMSE) and the cognitive section of the Cambridge Examination for Mental Disorders of the Elderly (6). Subjects scoring less than the standard cutoffs for global cognitive impairment on these measures (24 and 80, respectively) were excluded.

Subjects received a thorough psychiatric assessment by a senior psychiatrist and a semistructured interview by a research nurse. These data were reviewed by a senior research psychiatrist (A.T. or J.O.). We obtained information from the clinical history and physical examination regarding any previous strokes, transient ischemic attacks, myocardial infarctions, angina, hypertension, current systolic and diastolic blood pressure, diabetes mellitus (and current glucose), smoking, and cholesterol level. Both the Montgomery-Åsberg Depression Rating Scale and the 30-item Geriatric Depression Scale (7) were used to rate the severity of depression.

A blood sample from each subject was immediately taken on ice to the laboratory, where serum was aliquotted and frozen for later analysis. A sample was also sent for routine full blood count, biochemistry, and estimation of C-reactive protein. Subjects were required to have a normal blood count and biochemistry, with the upper cutoff for C-reactive protein set at 18.8 mg/liter in accordance with the recommendations of Wener et al. (8). Human IL-1β was measured in duplicate in serum samples by using a quantitative sandwich enzyme immunoassay (Amersham Biosciences UK Limited, Buckinghamshire, U.K.); plates were read at 450 nm. Intra-assay reliability, a measure of variability within each assay, was 7.6 for IL-1β.

Analyses of variance (SPSS version 10.0, Chicago) followed by unpaired t tests were used to examine group differences. Pearson's correlation coefficients were calculated to examine the relationship of depression severity to IL-1β levels. Post hoc correlation coefficients, t tests, or Mann-Whitney tests were used as appropriate to examine the effects of possible confounders.

Results

Nineteen subjects with major depression, 20 with subsyndromal depression, and 21 healthy comparison subjects met entry criteria (Table 1). Groups did not differ in age or sex; as expected, however, the depressed groups had greater cognitive impairment. There were differences in IL-1β across the groups, and analysis revealed this to be attributable to the significantly greater level of IL-1β (greater by 171%) in subjects with major depres-

TABLE 1. Comparison of Interleukin 1β in Subjects With Late-Life Major Depression, Subjects With Subsyndromal Depression, and Healthy Comparison Subjects

Characteristic	No Depression (N=21)		Major Depression (N=19)		Subsyndromal Depression (N=20)		Analysis[a]		
	Mean	SD	Mean	SD	Mean	SD	F	df	p
Age (years)	74.9	7.0	76.4	7.3	75.1	5.7	0.29	2, 57	<0.75
	N		N		N		χ^2	df	p
Sex							1.38	2	<0.51
Male	9		6		10				
Female	12		13		10				
	Mean	SD	Mean	SD	Mean	SD	F	df	p
Scores on measures of cognition and depression									
Mini-Mental State Examination	28.7	1.0	26.8	2.5	26.3	2.1	8.21	2, 56	0.001
Cognitive section of the Cambridge Examination for Mental Disorders of the Elderly	95.0	3.8	88.0	7.3	88.6	6.1	310.46	2, 56	<0.001
Montgomery-Åsberg Depression Rating Scale	1.1	1.5	30.3	6.2	12.0	5.3	190.93	2, 57	<0.001
Geriatric Depression Scale	2.8	2.5	20.9	4.2	15.4	7.9	43.57	2, 49	<0.001
C-reactive protein (mg/liter)	3.9	3.3	5.5	3.3	3.8	2.9	2.24	2, 55	<0.12
IL-1ß (pg/ml)[b]	1.0	1.2	2.7	2.5	1.8	1.8	4.53	2, 57	<0.02

[a] Comparisons made using analysis of variance or chi-square tests.
[b] Results of t tests: healthy subjects versus those with major depression (t=3.15, df=38, p=0.003); healthy subjects versus those with subsyndromal depression (t=1.54, df=39, p<0.14); subjects with major depression versus those with subsyndromal depression (t=1.41, df=37, p<0.17).

sion than in the normal comparison subjects. There were no differences between the group with subsyndromal depression and those with major depression or the healthy subjects. C-reactive protein levels did not differ among the groups.

Pearson tests revealed highly significant correlations between IL-1β and depression severity in the whole study group according to both Montgomery-Åsberg Depression Rating Scale (r=0.44, N=60, p<0.001) and Geriatric Depression Scale (r=0.41, N=52, p=0.003) scores. There was no gender difference in IL-1β levels in either the depressed groups or in all subjects (F<0.14, p>0.70). Although cognitive impairment was greater in the depressed groups, there was no correlation of IL-1β levels with scores on the MMSE or the cognitive section of the Cambridge Examination for Mental Disorders of the Elderly (p>0.8). There were no differences between the groups in vascular diseases and risk factors.

There was no correlation between the age at onset of first depressive episode and IL-1β level (r=0.04, N=36, p<0.83) or between people with an early onset of depression (first episode before age 60) (N=17) and those with a late onset of depression (N=19) (t=0.28, df=34, p<0.79). However, duration of current depressive episode (mean=30.16 weeks, SD=70.15) strongly correlated with IL-1β level (r=0.63, N=20, p=0.004); lifetime duration of depression (mean=68.67 weeks, SD=87.63) did not (r=0.17, N=12, p<0.61). Treatment with psychotropic or antiinflammatory medications or ECT was not associated with IL-1β level.

Discussion

As hypothesized, we found higher levels of IL-1β in subjects with current major depression and that IL-1β levels strongly correlated with current depression severity. The correlation suggests that the finding may be state related, and this suggestion is supported by the fact that IL-1β levels were correlated with the duration of the current depressive episode but not with the lifetime duration of depression.

To our knowledge, this is the first report of IL-1β levels in late-life depression, and our findings are consistent with those of Penninx et al. (3), who reported increases in the cytokines IL-6 and TNF-α in community subjects with late-life depression. Penninx et al. reported an association of IL-6 with male gender, but we found no such relationship with IL-1β. Our findings are also consistent with earlier reports of elevations of IL-1β in middle-aged depressed adults (1, 9); a correlation with current depression severity was also noted in another study (2). In our examination of the association between severity of illness and duration of current depressive episode, like Anisman et al. (2), we found a strong relationship, unlike the relationship between lifetime duration of depression and severity of illness.

This study was limited by its cross-sectional design and the absence of other important neurobiological measures in depression such as alterations in the hypothalamic-pituitary-adrenal (HPA) axis. It complements the report of Penninx et al. by examining hospital-derived psychiatry subjects and confirming higher levels of another cytokine. A

prospective analysis assessing IL-1β is necessary to confirm that a higher level of IL-1β is a state-related phenomenon.

The higher levels of IL-1β could be due to cerebrovascular disease with associated ischemia and inflammation, such as we have reported in late-life depression (4, 10); IL-1β might be leaking out across an impaired blood-brain barrier. Alternatively, cytokine increases have been associated with HPA axis dysfunction, and the increase in IL-1β may be mediated by this mechanism (3). An interaction between these mechanisms is possible because high levels of circulating cytokines (from prefrontal vascular disease) can activate the HPA system by direct hypothalamic effects or because elevated peripheral cytokines are thought to be able to mediate central inflammatory effects, starting with HPA axis dysfunction.

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