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ORIGINAL RESEARCH

Sustained inflammation 1.5 years post-stroke is not associated with depression in elderly stroke survivors

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Background: Depression is common in elderly stroke survivors and has been associated with systemic inflammation. We aimed to investigate an elderly population of Swedish stroke patients for evidence of sustained peripheral inflammation 18 months post-stroke and to identify if inflammation is associated with post-stroke depression at 18 months post-stroke.

Methods: The Barthel Index was used to measure the level of impairment in activities of daily living at 3 days post-stroke. Serum concentrations of inflammation markers, ie, C-reactive protein and white cell count, were measured in 149 stroke patients (mean age 81 ± 5.33 years, 35% male) at 18 months post-stroke, and a comparison was made with an age-matched sample of elderly Swedish individuals who had not suffered a stroke. At the same visit, clinical depression was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised criteria. Severity of depression was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: Mean C-reactive protein and white cell count levels in stroke patients were significantly elevated at 18 months post-stroke compared with population probands. Disability scores were associated with MADRS depression scores, but C-reactive protein and white cell count were not.

Conclusion: We found evidence for a sustained peripheral inflammatory response at 18 months post-stroke. C-reactive protein and white cell count were not associated with depression in this study.

Keywords: geriatric, inflammatory, ischemia, mood

Introduction

Ischemic and hemorrhagic stroke affects 16 million people worldwide annually, with the risk of stroke doubling with each decade of life after the age of 55 years.[1] Post-stroke depression is particularly common, affecting at least one third of all stroke patients, and adversely affecting the response to rehabilitation and quality of life.[2] A number of risk factors are associated with the presentation of post-stroke depressive symptomatology including stroke severity,[3] severity of stroke disability,[4] a history of prior stroke,[4] a history of clinical depression,[5] female gender,[4,6,7] single relationship status,[7] and cardiovascular disease.[6] Recent research on post-stroke depression has begun to focus on the association between depression and inflammation-mediated apoptosis.[8]

Ischemic stroke induces a central and peripheral inflammatory response.[9] The brain responds to ischemic injury with an acute and prolonged inflammatory response, characterized by rapid infiltration of microglia, upregulation of proinflammatory cytokines,

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and infiltration into the ischemic tissue.[10] Recruitment of neutrophils has been detected within the first 24 hours of adult stroke.[11] Macrophage recruitment starts later, with elevations seen at 3 days after stroke onset.[12] Peripheral inflammatory molecules, ie, interleukin (IL)-1β, IL-6, IL-18, and tumor necrosis factor alpha, are elevated within the first 24 hours, reach peak levels around 2–3 days, and remain elevated at 3 months post-stroke.[13–15] Peripheral C-reactive protein and white cell count are increased within 24 hours of stroke onset, correlate with infarct size, and remain elevated at even 3 and 12 months after stroke onset.[16] The current study aimed to identify whether there was evidence for sustained peripheral inflammation 18 months post-stroke, as defined by elevated C-reactive protein and white blood cell expression in peripheral blood samples, compared with an age-matched nonstroke cohort.

Upregulation of inflammatory cytokines has also been associated with clinical depression.[2] Relatively few studies have examined the association between inflammation and post-stroke depression. A recent study found a significant association between serum IL-18 measured at day 7 post-stroke and Montgomery-Asberg Depression Rating Scale (MADRS) depression scores at 2 weeks and 6 months after stroke onset.[17] Studies have also found nonsignificant trends for elevated C-reactive protein in patients with post-stroke depression measured within a month of stroke.[18–20] However, to our knowledge, no studies have examined the association between the inflammatory markers, C-reactive protein and white cell count, and depression in elderly stroke survivors as long as 1.5 years after stroke. Thus, it is important to clarify if these factors correlate with the post-stroke depression that has already been shown to affect at least a third of a much studied cohort of elderly stroke patients.[21,22] Given the risk factors described above, this study aimed to identify whether there was evidence for sustained peripheral inflammation 18 months post-stroke, as defined by elevated C-reactive protein and white cell count expression, in peripheral blood samples compared with an age-matched cohort and to identify if the inflammatory markers, C-reactive protein and white cell count, female gender, cardiovascular comorbidity, and impairment in activities of daily living post-stroke, are associated with post-stroke depression among chronic stroke survivors.

Materials and methods

Subjects and study protocol

Participants were selected from the Gothenburg 70+ Stroke study,[23] that included individuals aged at least 70 years who presented to Sahlgrenska University Hospital, Gothenburg, Sweden, between February 1, 1993 and May 17, 1994 with an acute focal neurological deficit of no other apparent cause than cerebrovascular events and confirmed by routine investigations and acute computed tomography scans. Patients were excluded if brain computed tomography showed extracerebral or subarachnoid hemorrhage or a cerebral tumor, or if the patient was comatose (n = 17, 20%). Patients were also excluded if they presented with symptoms beginning more than 7 days prior to admission, required specialized neurological care (n = 46, 53%), lived in a nursing home at the time of admission, or if there was no available bed in the stroke unit. Patients were later contacted by letter, and subsequently by phone, to arrange a hospital-based appointment 1.5 years after stroke. If unable to attend the hospital, the examination took place in the participants' homes (n = 15, 10%). Relevant medical information obtained from participants included risk factors for stroke, including history of previous stroke and cardiovascular disease (predating the index stroke). Informed consent was provided following written and verbal information to participants or their closest relatives. Ethics approval was granted by the ethics committee for medical research at the University of Gothenburg (33/94). Mean age at follow-up was 81 ± 5.33 (range 70.8–92.8) years.

Control reference data

Control participant reference data relating to C-reactive protein and white cell count were sourced from the National Health and Nutrition Examination Survey, 1999–2002, (n = 4472 men and 5212 women) and from the Cardiovascular Health Study (n = 2227 men and 2924 women), which are large population-based studies of community-dwelling elderly individuals aged 80 years and over.[24,25]

Biomarker collection

C-reactive protein was analyzed from venous blood samples taken at 1.5 years after stroke drawn into gel tubes, turned over at least five times, and centrifuged according to the manufacturer's specifications for 10 minutes after coagulation. Serum was separated and stored at room temperature until analysis with turbidimetry. White cell count was analyzed by automated particle count of white blood cells taken in ethylenediamine tetra-acetic acid tubes at 1.5 years after stroke.

Diagnostic criteria

Assessments of depression were conducted by a neurologist/psychiatrist (TL) unaware of lesion information at the time of or during the interview (1.5 years after

stroke). Clinical depression was diagnosed according to DSM-III-R (Diagnostic and Statistical Manual Of Mental Disorders, Third Edition-Revised)[26] criteria. Depressive symptomatology was assessed using the MADRS.[27] The diagnostic procedure involved a consensus conference with a second neurologist and psychiatrist prior to determination of final diagnoses. The Barthel Index was used as a functional measure of independence in activities after stroke.[28]

Statistical methods

The statistical analysis was conducted using the SPSS version 18 package (SPSS Inc, Chicago, IL). Preliminary analyses were performed to ensure assumptions of normality, linearity, and homoscedasticity were met. When assumptions were violated, square-root transformations were performed to maintain a normal distribution. Transformed variables included C-reactive protein values and MADRS depression scores. All statistical analyses were performed using the transformed values. Hierarchical multiple regression was used.

Results

Characteristics of observational cohort study population

Table 1 shows the characteristics of stroke survivors. Of the 243 patients at stroke admission, 32% (n = 77) had passed away while 7% (n = 17) declined to participate, leaving 149 volunteer patients at the 1.5-year follow-up. Of those participating, 66% were female (n = 67) and 34% were male (n = 35). Mean age at follow-up was 81 ± 5.33 (70.8–92.8) years. Female MADRS scores were one point higher than those observed among male participants. A higher percentage of men than women were diagnosed with major depression (17.1% versus 10.4%) and depressive disorder not otherwise specified (DDNOS, 8.6% versus 4.4%). More females were diagnosed with dysthymia (16.4% versus 2.9%). Stroke disability scores were more severe among women than in men. More male than female participants had recurrent stroke (25.7% versus 10.4%) and cardiovascular disease (25.7% versus 23.9%). C-reactive protein levels and white cell counts were comparable between male and female participants.

Comparison of study population with literature-sourced control data

Independent-samples *t*-tests show that stroke survivors had significantly higher C-reactive protein levels ($t[101] = 3.58$, $P = 0.001$) and white cell counts ($t[101] = 2.21$, $P = 0.029$) than individuals not affected by stroke.

Table 1 Patient characteristics

	n	Mean (SE) or % (n)	Median
Female			
Age, years	67	82.1 (0.62)	83.07
MADRS	67	11.24 (1.06)	9
Major depressive episode	67	10.4% (n = 7)	
Dysthymia	67	16.4% (n = 11)	
DDNOS	67	4.4% (n = 3)	
Stroke disability – mild	67	92.5% (n = 62)	
Stroke disability – moderate	67	4.5% (n = 2)	
Stroke disability – severe	67	3.0% (n = 2)	
Previous stroke	67	10.4% (n = 7)	
Previous heart disease	67	23.9% (n = 16)	
CRP (mg/L)	67	2.83 (0.10)	2.57
WCC (10^9/L)	67	6.72 (0.23)	6.60
Male			
Age, years	35	79.70 (0.76)	79.98
MADRS	35	10.15 (1.58)	7
Major depressive episode	35	17.1% (n = 6)	
Dysthymia	35	2.9% (n = 1)	
DDNOS	35	8.6% (n = 3)	
Stroke disability – mild	35	85.7% (n = 30)	
Stroke disability – moderate	35	14.3% (n = 5)	
Stroke disability – severe	35	0% (n = 0)	
Previous stroke	35	25.7% (n = 9)	
Previous heart disease	35	25.7% (n = 9)	
CRP (mg/L)	35	2.71 (0.14)	2.45
WCC (10^9/L)	35	6.40 (0.26)	6.20

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; DDNOS, depressive disorder not otherwise specified; CRP, C-reactive protein; WCC, white cell count.

Analysis of depression

Stroke patients diagnosed with depression had higher mean values for C-reactive protein and white cell count than those without depression (10.44 versus 10.17 for C-reactive protein and 6.85 versus 6.47 for white cell count). However, there was no significant difference in levels of C-reactive protein or white cell count between stroke patients diagnosed with major depression, dysthymia, or DDNOS and those that were not ($t[101] = 0.09$, $P = 0.932$ and $t[101] = 1.04$, $P = 0.303$, respectively).

Table 2 shows the nonstandardized (B) and standardized (β) regression coefficients, the standard error of the coefficients (SE B), and the change in R^2 after entry of each additional block of independent variables to the regression. To control for gender and stroke disability, which are strongly associated with post-stroke depression,[3,6] these variables were entered together into the first block. Cardiovascular

Table 2 Results from hierarchical multiple regression analysis

	B	SE B	β	R^2
Step 1				0.087
Constant	5.23	0.76		
Gender	–0.50	0.26	–0.18	
Stroke disability	–0.62	0.27	–0.22*	
Step 2				0.049
Constant	5.10	0.75		
Gender	–0.58	0.26	–0.21*	
Stroke disability	–0.63	0.26	–0.23*	
Previous heart disease	0.61	0.29	0.20*	
Previous stroke	0.37	0.37	0.10	
Step 3				0.013
Constant	4.94	0.94		
Gender	–0.56	0.26	–0.20*	
Stroke disability	–0.66	0.26	–0.24*	
Previous heart disease	0.63	0.29	0.20*	
Previous stroke	0.37	0.36	0.10	
CRP (mg/L)	0.19	0.16	0.12	
WCC (10^9/L)	–0.05	0.07	–0.06	

Notes: Nonstandardized (B), and standardized (β) regression coefficients, standard error of coefficients (SE B), and change in R^2 after each block of independent variables associated with depression at 1.5 years post-stroke, $R^2 = 0.01$ for step 1, and 0.00 for steps 2 and 3. *$P < 0.05$.
Abbreviations: CRP, C-reactive protein; WCC, white cell count.

disease and previous stroke have also been identified to correlate highly with post-stroke depression, and therefore were entered into block two. The third block consisted of C-reactive protein and white cell count. Gender and stroke disability explained 8.7% of the variance in depression scores, with stroke disability contributing significantly to MADRS depression scores ($t = –2.34$; $P = 0.02$). Addition of cardiovascular disease and previous stroke explained an additional 4.9% of the variance in MADRS depression scores (the model as a whole explained a total of 13.6%), with a history of cardiovascular disease significantly predicting MADRS depression scores ($t = 2.09$; $P = 0.04$). Addition of C-reactive protein and white cell count explained an additional 1.3% of the variance in depression scores (the total amount explained by the model was 14.9%), but C-reactive protein and white cell count were not independently associated with MADRS depression scores.

Discussion

To our knowledge, this is the first observational cohort study to examine the relationship between peripheral inflammation and depression in elderly stroke survivors at 1.5 years after stroke. We provide evidence of a sustained peripheral inflammatory response characterized by elevated levels of C-reactive protein and total white cell count at 18 months after stroke. This is consistent with previous research indicating that C-reactive protein and white cell count are elevated at 3 and 12 months after stroke.[9,29] It is also consistent with a study involving immunohistopathological characterization of inflammatory molecule expression in 137 cases of post-mortem human cerebral infarct (where the age of lesions ranged from one day to 53 years after stroke onset), suggesting that chronic inflammation may persist for years after stroke onset.[12] Our results also showed that cardiovascular comorbidity was associated with depression at 18 months post-stroke. Many risk factors for stroke, such as diabetes, hypertension, and atherosclerosis, are associated with elevated inflammatory profiles.[30] Thus, it is likely that stroke patients have a pre-existing hyperinflammatory state that is associated with ischemic risk and recurrent stroke.[31]

Our analyses showed that, while C-reactive protein and white cell count were elevated among stroke survivors, these factors were not associated with MADRS depression scores or depression diagnosis (using DSM-III-R criteria for major depression, dysthymia or DDNOS). While different from some studies conducted in the general population, these results are consistent with results from other studies in patients with cardiovascular disease.[32] Results are also consistent with our recent meta-analysis showing no association of post-stroke depression with a variety of inflammatory mediators measured within one month after stroke (C-reactive protein, IL-18, IL-6, or tumor necrosis factor alpha).[33] In particular, Jimenez et al,[34] McKechnie et al,[20] and Rothenburg[35] found nonsignificant trends for higher levels of C-reactive protein in patients (recruited from stroke units) with post-stroke depression, measured 10–35 days after stroke onset and defined using DSM-IV (Diagnostic and Statistical Manual Of Mental Disorders, Fourth Edition, Text Revision) diagnostic criteria or by a cutoff score on the Center for Epidemiologic Studies Depression scale. White cell count has not previously been studied in relation to depression in stroke survivors. A recent study of the proinflammatory cytokine, serum IL-18, showed that serum IL-18 measured at 7 days was significantly associated with MADRS depression scores at 2 weeks and 6 months after stroke onset (n = 100).[17] However, studies with fewer participants (n = 30 and n = 47) and using DSM-IV diagnostic criteria to classify depression report nonsignificant trends for an association of IL-18 levels and post-stroke depression in the first 10 days after stroke.[35,36] Trends for associations of other proinflammatory cytokines (IL-6 and tumor necrosis factor alpha) with post-stroke depression have also been reported at 7–30 days post-stroke.[17,19,34] As expected, impairment in activities of daily living at 3 days after stroke onset independently predicted MADRS depression scores. This is consistent with previous research indicating that the level of

post-stroke impairment predicts depression at 3,[37] and 6 and 12[3] months post-stroke.

One strength of our study, is the thorough diagnostic workup in stroke patients. However, an important methodological limitation is that these data were collected in the 1990s, so DSM-III-R criteria were used to diagnose depression. Few studies have compared the diagnostic classification systems in relation to major depression. In a study of 176 outpatients with unipolar depression, DSM-III-R criteria diagnosed more patients with melancholia (22.7%) than DSM-IV criteria (16.5%).[38] In another study of 65 patients with unipolar depression, melancholic depression was diagnosed more frequently using DSM-IV (56.9%) than DSM-III-R criteria (50.8%).[39] Thus, some misclassification was inevitable. Our findings would benefit from replication with more markers of inflammation and with repeated measures of inflammatory markers in the same cohort. Measurement of inflammatory markers was performed on one occasion in this study. The results would be considered more robust with repeated measures of inflammatory markers over a period of time. While efforts were made to control for potentially confounding variables, infarct volume and brain volume were not available for assessment to add to our model.

Conclusion

The current study aimed to identify whether there was evidence for sustained peripheral inflammation 18 months following stroke as defined by elevated C-reactive protein and white cell count expression in peripheral blood samples compared with an age-matched cohort and to identify if the inflammatory markers, C-reactive protein and white cell count, were associated with post-stroke depression among chronic stroke survivors. In this study, elderly stroke survivors had elevated inflammatory markers 18 months post-stroke compared with age-matched population controls. However, this increased inflammatory state was not associated with depressive disorders, and thus cannot explain the increased prevalence of depression after stroke or distinguish those at an increased risk of depression.

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Disclosure

The authors report no conflicts of interest in this work.

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