The long term prognosis of patients with major depression and silent cerebral infarction

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Short title: Long term prognosis of patients with depression and SCI

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Abstract

OBJECTIVE: Many studies have examined the effects of cerebrovascular change on treatment response in geriatric depression. However, few such studies have examined the relationship between cerebrovascular changes and long term prognosis. We examined the effects of cerebrovascular change on the course of geriatric depressive symptoms, dementia rates, and mortality over a follow-up period of approximately 10 years.

METHOD: Participants were 84 patients with major depression (age of onset greater than 50 years old); patients suffering from strokes, neurological disorders, and other psychiatric disorders were excluded. MRI findings were used to classify all patients into silent cerebral infarction (SCI) positive (n = 37) or negative groups (n = 47). Patient prognoses were ascertained using a review of clinical charts and over the mail.

RESULTS: Only 5% of patients with SCI were able to maintain remission, whereas 36% of those patients without SCI were able to do so. Total duration of depressive episodes was significantly longer in the SCI positive group than in the SCI negative group. In addition, SCI was associated with a higher risk of the onset of dementia.

CONCLUSION: The results of this long-term follow-up study demonstrate that the presence of SCI is associated with a relatively poor prognosis for geriatric depression.

Introduction

A growing body of evidence supports an association between cerebrovascular disease (CVD) and geriatric depression (1-4). The term "vascular depression" has been used to describe a subtype occurring later in life and characterized by brain changes that may be related to depression onset.

Previously, we examined the relationship between geriatric depression and the presence of silent cerebral infarction (SCI), as detected by magnetic resonance imaging (MRI). SCI is detectable by MRI and other imaging modalities but has not been associated with the occurrence of strokes, focal neurological symptoms, or dementia. Depressive patients with SCI appear to closely resemble those with vascular depression. Our earlier findings suggest that depressed patients with SCI show poor treatment responses to antidepressant pharmacotherapy, relative to depressed patients without SCI (5-7). Other researchers have also demonstrated a relatively poor prognosis and increased mortality of geriatric depressive patients with CVD (8). Cognitive impairment in elderly depressed patients with CVD has also been reported, both during the depressed phase of the illness (9) as well as after recovery (10). However, to our

knowledge the relationships between the presence of CVD and two key variables, long term prognosis and onset of dementia, have not been investigated in elderly depressed patients.

We aimed to test the following hypothesis: Patients with depression and SCI will have higher rates of recurrence, dementia onset, and mortality than depressive patients without SCI.

Method

This study was designed in accordance with institutional guidelines and was approved by an institutional ethics review committee. All participants gave their written informed consent to take part in this study.

Participants

We initially assessed 172 patients with unipolar depression (meeting DSM-III-R or DSM-IV criteria for a major depressive episode), all of who were over 50 years old. All patients were first admitted to either the Hiroshima University School of

Medicine or Hiroshima Prefectural Hospital during the period of 1990 to 1999.

The patients included in this study were examined using MRI within three months of admission, and all met either the DSM-III-R criteria for major depression (11) or the DSM-IV criteria for major depressive disorder (12). Patients showing evidence of stroke or focal neurological signs were excluded from the study. In addition, patients with alcoholism, cerebral degenerative disease, dementia, brain injury, systemic disease, and those taking medications that could induce depression were also excluded.

Eighty-nine patients were followed for the course of the study (representing 52% of the original sample assessed). Eighty-three patients had stopped receiving treatment within 5 years of their admission dates and did not elect to participate over the entire course of our study. Of the remaining 89 patients, we randomly selected 84 patients in a blind manner, matching for age and sex across the two groups. There were no significant differences between the patients who provided complete data and those who did not on the variables of age, sex, age of depression onset, and proportion of patients with SCI.

Magnetic resonance imaging procedure

MRI was performed using a 1.5-T apparatus (General Electric Co., Milwaukee, WI, USA) at the Hiroshima University School of Medicine and an 0.5-T apparatus (Picker Co.) at the Hiroshima Prefectural Hospital. T2-weighted images (repetition time TR, 4000 ms; echo time TE, 100 ms) were obtained in the transverse plane parallel to the orbitomeatal line, and T1-weighted images (TR, 400 ms; TE, 14 ms) were obtained as coronal slices at a 5-mm thickness, with a 2.5-mm gap between sections. Infarcts were defined as high-intensity lesions that were larger than 5 mm in diameter, on T2-weighted images that coincided with low-intensity T1-weighted lesions.

In the present study, as in our previous reports, a silent cerebral infarction was defined as the presence of four or more infarcts in the same hemisphere, and these patients were assigned to the SCI (+) group (5-7, 10, 13). Patients with fewer than four infarcts were assigned to the SCI (-) group. Periventricular hyperintensity was not assessed. Details regarding the location and the particular hemisphere containing the SCI were not assessed, given that almost all of the patients possessed multiple lesions. MRI scans were combined in a randomized order and were evaluated by a research psychiatrist (T.F.) prior to data collection.

Outcome measures

Three main outcomes were assessed: Course of depressive symptoms, dementia onset, and mortality. Reviews of patients' clinical charts were used to assess outcomes. In addition, all patients and their family members underwent detailed questioning by mail. The required minimum follow-up period for this study was five years. Patients who stopped receiving treatment within 5 years (such that the clinical courses of these patients after stopping treatment were unknown) were excluded from data analysis.

We examined number of relapses/recurrences, duration of depression, and the number of admissions for the purpose of treating unipolar depression. The presence of manic episodes, either spontaneous or induced by antidepressant treatment, was also examined. Finally, the incidence of neurological disorders other than stroke (such as parkinsonism), the incidence of delirium, onset of dementia, and mortality were examined. The DSM-IV definition of dementia was used (12).

Analytic strategy

Parametric data are reported as the mean $\pm$ SD. The Student's t-test

was used to compare mean differences between the groups. The χ^2 test was

used to compare nonparametric numerical data points. A p-value of < 0.05 was

considered statistically significant.

Results

There were no significant differences between the patients with SCI and those

without on the variables of age, sex, age of depression onset, years of education, kind of

MRI acquisition (1.5 tesla or 0.5 tesla), duration of study follow-up period, and kind of

follow-up used (clinical chart, questionnaire by mail, or both)　(Table 1).

Prognosis of affective disorders

Prognosis data for our study sample are shown in Table 2. Only 5% of

patients with SCI could sustain remission, although 36% of those patients without SCI

were able to do so. Number of depressive episodes during the follow-up period was not

significantly different across the groups. However, total duration of depressive episodes,

percentage of depressed periods during follow-up, and number of hospital admissions

due to depression were all greater in patients with SCI than in those patients without

SCI. The two groups did not differ based on the presence of manic episodes.

Other disorders and mortality

There were no significant group differences in the numbers of patients who

developed delirium, stroke, and Parkinsonism during follow-up. Mortality rates did not

differ across the groups. However, the dementia onset rate during follow-up was

significantly higher in patients with SCI than in those patients without SCI.

Discussion

While there are several reports on the effects of cerebrovascular change on

treatment response in geriatric depression, to our knowledge no previous report has

addressed the relationship between cerebrovascular changes and long term prognosis of

geriatric depression.

In the present study, only 5% of patients with SCI could remain in remission

during the follow-up period, whereas 36% of the patients without SCI continued

remission. Total duration of depression was significantly longer in the SCI positive

group than in the SCI negative group. In addition, SCI was associated with a higher risk of developing dementia.

The present results are consistent with the findings of previous studies that examined treatment responses in geriatric depression. Post (14) found that only 26% of a sample of 92 elderly depressed inpatients made a sustained recovery during a 3-year follow-up period: 25% of patients continued to experience chronic, mild depression, and 12% were continuously ill throughout the follow-up period. Murphy (15) reported that 35% of a sample of 124 elderly depressed patients (> 65 years of age) had a good outcome; 19% relapsed, 29% were continuously ill, 3% developed dementia, and 14% died. Murphy (15) concluded that geriatric depression is associated with poor treatment response relative to depression in younger patients. However, neither Post nor Murphy addressed the presence of organic brain disease.

Concerning the effects of cerebrovascular changes on the course of depressive symptoms, Simpson et al. (16) conducted a 24-week naturalistic study of the treatment of geriatric depression. They reported that subcortical hyperintensities were more numerous in treatment resistant patients, and that neuropsychological impairment was

restricted to such patients. We also earlier noted a relationship between the presence of cerebrovascular changes and poor treatment response to antidepressant therapy (5, 7), as well as relatively poor prognosis in these patients during a three-year follow-up period (6). On the contrary, Krishnan has investigated 6-month recovery from an index episode of major depression in subjects with and without MRI-confirmed vascular brain changes. They reported no significant differences in course between patients with and without vascular depression (17). However, most of these earlier studies involved follow-up periods of less than five years and did not address dementia rates.

The mechanism that underlies the poor long-term prognosis of affective disorders in patients with SCI remains unclear, but one possible explanation is that the relatively poor cognitive functioning of these patients is itself associated with poor long-term prognosis. Baldwin et al. (18) showed that resistance to treatment of late-onset depression may be associated with impaired executive functioning, and they speculated that subtle cerebrovascular mechanisms might underlie this cognitive impairment. Cognitive impairment in elderly depressed patients with CVD has been reported during the depressive phase of the illness (9) as well as after recovery (10).

This study demonstrated that onset rates of dementia are significantly higher in patients with SCI than in those patients without.

Concerning the relationship between dementia and depression, Hebert et al. (19) investigated cohort incidence rates of vascular dementia by following 8,623 subjects over a 5-year period. They identified a number of risk factors for this form of dementia, including age, depression, diabetes, hypertension, heart problems, taking aspirin, and others. These researchers speculated that previous episodes of depression could represent a premonitory syndrome for vascular dementia or a marker of the importance of cerebral damage. Kokmen (20) reported that previous episodes of depression and hypertension increase incidence rates of Alzheimer's disease. However, they did not initially examine the existence of vascular pathology using a neuroimaging modality, such as computed tomography or magnetic resonance imaging.

Although little is known about the pathophysiological mechanism underlying this association, a growing number of reports demonstrate that depression may affect the coagulation system, thereby increasing risk of stroke (21). One possibility is that previous or current episodes of depression may affect preexisting SCI and thereby

increase dementia risk.

Incidence rates of dementia in the general population aged from 60-70 years old have been reported as 1 to 6 persons per 1,000 person years (22-24). The incidence rate of dementia in the present SCI (-) group was about 4 persons per 1,000 person years. Previous episodes of depression alone may exert little effect on dementia onset, although the coexistence of depression and SCI appears to constitute a potentially deadly combination.

A major limitation of our study is the lack of a comparison group in the form of non-depressed controls. Future studies should include such a group to strengthen any potential findings. We were not able to assess dementia onset risk associated with the presence of SCI or depression alone, nor were we able to examine the two synergistically.

A second limitation is the lack of treatment data for this cohort during the follow-up period. Chronic exposure to medications may have neuroprotective or neurotrophic effects in some regions, including the basal ganglia, hippocampus, and subgenual anterior cingulate (25), and the anticholinergic effects of antidepressants may

worsen cognitive functioning (26). We therefore cannot exclude potential medication effects on the present findings.

A third limitation was our use of different magnet field strengths to detect infarcts. The lower field strength of 0.5T results in more false negative findings relative to the 1.5T magnet. However, we believe that this difference exerted a minimal effect on our results, given that the proportion of participants tested with the 0.5T magnet did not differ across the SCI positive and negative groups.

We conclude that among elderly patients with major depression, the presence of SCI is associated with a relatively poor prognosis. In addition, presence of SCI is a risk factor for onset of dementia among patients with geriatric depression.

Additional studies are needed to replicate these findings and to elucidate mechanisms. In particular, studies will need to account for location of cerebrovascular change, type of dementia, and should examine ongoing treatment of depression and co-morbid medical illness.

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Table 1

Characteristics of depressed patients

	SCI (-) group (n=47)	SCI (+) group (n=37)	*p*-value
Male/ Female	18/29	13/24	0.77
Age, start of follow up	60.2±6.5	63.0±6.7	0.05
range	53-74	52-74	
Age, end of follow up	70.3±6.9	71.8±7.4	0.35
range	59-87	60-87	
Years of follow up	10.1±3.6	8.7±3.3	0.06
range	5-15	5-15	
Kind of follow up			0.95
Clinical chart	29	24	
Questionnaire by mail	4	3	
Both	14	10	
Age at onset of depression	56.3±7.2	56.8±9.0	0.78
range	50-70	50-71	
Type of MRI acquisition			0.49
1.5T	41	34	
0.5T	6	3	
Years of education	11.8±2.5	11.8±2.4	0.91
range	6-16	6-16	

Table 2

Prognosis of affective disorders

	SCI (-) group	SCI (+) group	p-value
Continue remission	17 (36%)	2 (5%)	< 0.001
Number of depressive episodes	1.4±3.8	2.3±2.4	0.24
Total duration of depression (y)	1.3±2.1	2.5±2.2	0.02
Percentage of years depressed	16.0±27.1	34.8±30.3	0.007
Number of admissions due to depression	0.4±0.7	1.0±1.3	0.008
Presence of manic episode(s)	3 (6%)	6 (16%)	0.15

Table 3

Other disorders and mortality

	SCI(-) group	SCI(+) group	p-value
Mortality	6 (13%)	7 (19%)	0.44
Dementia	2(4%)	7(19%)	0.04
Delirium	0 (0%)	2 (5%)	0.11
Stroke	3 (6%)	6 (16%)	0.15
Parkinsonism	3 (6%)	5 (14%)	0.27
Number of co-morbid somatic diseases	0.5±0.7	0.8±1.0	0.17