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ORIGINAL PAPER

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Prospective study of major depressive disorder with white matter hyperintensity

Comparison of patients with and without lacunar infarction

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Abstract *Objective* To investigate clinical characteristics, outcome, and risk factor for cerebrovascular disease in patients who had major depressive disorder and white matter hyperintensity (WMHI). *Method* A total of 123 new patients diagnosed with major depressive disorder by semi-structured interview underwent magnetic resonance imaging (MRI) and were placed into one of three groups based on results. Patients with no abnormal findings (NF), patients with WMHI and no lacunar infarction (WMHI), and patients with lacunar infarction (LI). *Results* In the WMHI group, age at initial onset of depression and age at time of interview were both higher than in the NF group, as was severity of depression. Hamilton Rating Scale for Depression (HRSD) scores were significantly higher in the WMHI group than in the NF group. Total WMHI was significantly correlated only with age at initial onset of depression and age at time of interview. In the WMHI group, age at interview was lower than in the LI group and systolic and diastolic blood pressures were lower. Survival analysis regarding the clinical outcome of remission was conducted, but no significant differences were discovered among the three groups, WMHI, LI, and NF. However, the suicide rate was significantly higher in the LI group than in the other two groups. *Conclusions* The origin and clinical characteristics of depression accompanied by WMHI may be specific; additional stringent study in comparison with individuals with LI is needed.

Key words blood pressure · depression · MRI · suicide · white matter hyperintensity

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Introduction

White matter hyperintensity (WMHI), visualized on T_2-weighted magnetic resonance imaging (MRI) is observed more frequently among people with depression than individuals without psychiatric illness [4, 9, 15]. Points of contention on the relationship between depression and WMHI exist: Greenwald et al. [8] asserted that a relationship exists with hypertension or other risk factors for cerebrovascular disease; Awad et al. [1] hypothesized that age, prior history of cerebrovascular disease, and hypertension are risk factors for WMHI. O'Brien et al. [15] asserted that cerebrovascular disease cannot explain all cases of patients with depression WMHI. Particular clinical interest has focused on the association between WMHI and symptoms of depression [16, 17], cognitive dysfunction [14, 19, 20], and adverse effects and treatment response to antidepressant medication [3, 7, 10, 17, 18]. However, identification in many reports of WMHI only in T_2-weighted image suggests a high possibility that the population of patients with WMHI includes cases with silent cerebral infarction, indicated by low-signal intensity in T_1-weighted images, and this notion has added turmoil to the larger discussion over WMHI.

In the current study, we investigated clinical characteristics and response to treatment in patients with depression free from abnormal findings on MRI,

in patients with depression and cerebral infarction, and in patients with depression and WMHI strictly defined to exclude individuals with silent cerebral infarction.

Patients and methods

Subjects were recruited from consecutive patients seen initially in the Oita University Hospital, Department of Neuropsychiatry between October 28, 1998 and January 31, 2003 who were diagnosed with current major depressive disorder based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), and also cleared exclusion criteria. The exclusion criteria were as follows: ① central nervous system disorders and medical disorders clearly affecting cerebral function, ② pregnancy, ③ mental retardation, ④ severe language or auditory dysfunction, ⑤ age less than 17 years, and ⑥ high risk of suicide. We also excluded people with psychiatric disorders such as bipolar disorder, substance abuse or dependence, psychosis, and anxiety disorder. Study design was approved by the Oita University Ethics Committee, and informed consent was obtained from each participant before entry into the study.

Patients underwent imaging within 2 weeks after the interview with use of a 1.5-Tesla Siemens Magnetom Impact MRI Scanner (Siemens, Tokyo, Japan). The imaging method used was high-speed (SE). The images obtained for the study were axial, coronal, and sagittal T_1-weighted images, T_2-weighted images, and FLAIR images of 8 mm thickness (2.5 mm gap).

Images were analyzed by a radiologist who was blinded to clinical data. WMHI was defined as a macular region with indistinct margins in the white matter, detected by high-signal intensity in FLAIR images and isosignal intensity in T_1-weighted images. Lacunar infarction (LI) [2] was defined as a region with a 5-mm or greater diameter that demonstrated high-signal intensity in FLAIR images and low-signal intensity in T_1-weighted images. Other pericerebrovascular voids and artifacts were excluded. WMHI was classified according to site as periventricular WMHI (PVH), deep WMHI (DWMHI), or basal ganglion WMHI. Evaluation was also carried out for the left and right hemispheres using the evaluation scale of Fazekas [6]. PVH evaluation scores were 0 = absent, 1 = caps or pencil-thin lining, 2 = smooth halo, 3 = irregular PVH extending into the deep white matter; DWMHI evaluation scores were 0 = absent, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent areas. Due to the small number of patients in whom basal ganglion WMHI was observed, it was not evaluated. Ultimately, PVH evaluation scores of 0–3 for the left and right hemisphere and DWMHI evaluation scores of 0–3 for the left and right hemispheres were added to produce a total WMHI evaluation score (TWMHI) of 0–12 for each individual. Individuals with atypical findings other than WMHI and LI were excluded from analysis.

At the initial interview, the assessments performed were the 17-item Hamilton Rating Scale for Depression (HRSD), the Global Assessment of Functioning (GAF), and risk factors for cerebrovascular disease (systolic blood pressure, diastolic blood pressure, history of hypertension, lifetime alcohol consumption, and lifetime smoking). At 1-week intervals thereafter, the HRSD was completed and adverse drug effects were assessed. The severity of hypertension history was evaluated on a 5-point scale. Lifetime alcohol consumption was calculated as total intake of alcohol to the date of assessment based on self-declaration. Lifetime smoking was calculated as the number of cigarettes smoked to the date of assessment based on self-declaration. We measured cholesterol and triglyceride levels at the initial interview.

The antidepressant treatment chosen for the study was imipramine (dose up to 150 mg/day) administered for at least 4 weeks. If sufficient response was not obtained, gradual conversion to another agent was made. Remission was defined as an HRSD score of 7 or lower and a GAF score of 71 or higher that continued for one or more week.

Statistical analysis used analysis of variance (ANOVA), Sheffe test, Chi-square test, Pearson correlation analysis, survival analysis, and the Fisher exact test. The level of significance was defined as $P < 0.05$. The Sheffe testing was performed only when ANOVA demonstrated a significant difference among the three groups. Survival curves for time to recovery and time to study dropout (interval from randomization until the last research observation) were compared using the Kaplan–Meier product-limit formula [11, 12]. Cox proportional hazards models were used to assess the dropout's effect [5]. Furthermore, we performed a general descriptive discriminant analysis for detecting the variables that allow us to discriminate between naturally occurring different patient groups, and also to classify cases into different groups with better than chance accuracy. We tried to discriminate between the NF, WMHI and LI groups to determine whether the three subtypes had differentiating WMHI and LI, by using individual age in onset and age of examination as predictors of membership in the NF, WMHI and LI groups.

Results

The study evaluated a total of 123 patients (51 men, 72 women; mean age, 49.5 years; range, 17–83 years). Among participants 55 patients had neither WMHI nor LI (NF group: 24 men, 31 women), 46 had WMHI but no LI (WMHI group: 19 men, 27 women), and 22 had lacunar infarction (LI group: 8 men, 14 women).

Total WMHI scores were 3.93 in the WMHI group and 7.14 in the LI group ($P < 0.001$). Total PVH scores were 2.53 in the WMHI group and 3.67 in the LI group ($P < 0.05$). Total DWMHI scores were 1.24 in the WMHI group and 3.38 in the LI group ($P < 0.001$). All three differences were significant. The significant differences were similar to those obtained in inter-group comparisons for the left and right hemispheres, respectively (Table 1). On MRI, WMHI in the basal ganglion was observed in two patients in the WMHI group and in three patients in the LI group.

Age at initial onset of depression in the NF, WMHI, and LI groups was 37.3, 45.8, and 54.6 years, respectively. Age was significantly higher in the WMHI group ($P < 0.05$) and the LI group ($P < 0.01$) compared with the NF group, but there was no significant difference was not observed between the WMHI and LI groups (Table 1).

Age at time of interview in the NF, WMHI, and LI groups was 41.5, 50.8, and 63.8 years, respectively. Age at time of study participation was significantly higher in the WMHI group ($P < 0.01$) than in the NF group and was significantly higher in the LI group than in the NF group ($P < 0.01$) and the WMHI group ($P < 0.01$) (Table 1). The Wilks' Lambda value, indicating the degree of separation in the ages of three groups, was 0.721, $F(4, 238) = 10.60$, df = 2, $P < 0.0001$.

Systolic blood pressure was significantly higher in the LI group than in the NF group ($P < 0.01$) and the WMHI group ($P < 0.05$). However, a significant difference was not observed between the NF group and the WMHI groups. Diastolic blood pressure was sig-

Table 1 Subject characteristics: HRSD = Hamilton Rating Scale for Depression; T = Total; WMHI = White Matter Hyperintensity; PVH = Periventricular WMHI; R = Right; L = Light; NF = No abnormal Findings; LI = Lacunar Infarction

	NF group $N = 55$ Mean (SD)	WMHI group $N = 46$ Mean (SD)	LI group $N = 22$ Mean (SD)	ANOVA P	Sheffe
The age at initial onset	37.3 (14.0)	45.8 (14.9)	54.6 (16.1)	0.000	NF < WMHI[b], NF < Li[c]
Age at the time of interview	41.5 (14.2)	50.8 (14.0)	63.8 (10.3)	0.000	NF < WMHI, NF < LI, WMHI < Li[c]
Systolic blood pressure	116.0 (16.0)	120.5 (18.0)	136.7 (26.3)	0.002	NF < Li[c], WMHI < Li[b],
Diastolic blood pressure	72.9 (12.1)	71.8 (15.1)	85.3 (13.7)	0.005	NF < Li[b], WMHI < Li[c]
Severity of hypertension (0–5)	0.15 (0.5)	0.4 (0.8)	0.7 (0.9)	0.004	–
	198.6 (38.0)	201.1 (39.4)	196.1 (41.2)	0.880	–
Triglyceride	122.8 (85.0)	125.6 (104.0)	81.8 (30.7)	0.120	–
Lifetime smoking	46.8 (79.6)	125.3 (444.2)	49.3 (129.6)	0.366	–
Lifetime alcohol consumption	356.7 (1636.1)	10.2 (27.2)	22.5 (37.9)	0.263	–
Family history of mood disorder (Y/N)	7/48	6/40	2/20	0.885[a]	–
Number of prior depressive episodes	0.5 (0.9)	0.6 (2.0)	1.2 (3.0)	0.272	–
Total days of prior depressive episodes	67.4 (155.1)	125.7 (411.5)	105.9 (167.3)	0.582	–
Melancholia, yes/no	35/20	31/15	13/8	0.884[a]	–
HRSD	18.1 (5.7)	21.1 (5.4)	20.5 (5.6)	0.020	NF < WMHI[b]
T WMHI	–	3.9 (2.9)	7.1 (3.3)	0.000	
T PVH	–	2.5 (1.5)	3.7 (2.0)	0.031	
R PVH	–	1.3 (0.8)	1.8 (1.0)	0.013	
L PVH	–	1.3 (0.8)	1.9 (1.1)	0.013	
T DWMHI	–	1.2 (1.4)	3.4 (1.6)	0.000	
R DWMHI	–	0.7 (0.8)	1.8 (0.8)	0.000	
L DWMHI	–	0.7 (0.8)	1.6 (1.0)	0.000	

[a] Chi-square test; [b] $P < 0.05$; [c] $P < 0.01$

nificantly higher in the LI group than in the NF group ($P < 0.05$) and the WMHI group ($P < 0.01$). Again, a significant difference was not observed between the NF and WMHI groups. ANOVA demonstrated significant differences among the NF, WMHI, and LI groups in history of hypertension ($P < 0.005$), but multiple comparisons demonstrated no significant differences among groups. No significant differences were observed among the NF, WMHI, and LI groups in risk factors for cerebrovascular disease, namely, total cholesterol, triglycerides, lifetime smoking, and lifetime alcohol consumption (Table 1).

No significant differences were observed among the NF, WMHI, and LI groups regarding family history of mood disorder (Y/N), number of prior depressive episodes, total days of prior depressive episodes, and occurrence of melancholic features (Table 1).

Hamilton Rating Scale for Depression scores were significantly higher in the WMHI group than in the NF group ($P < 0.05$), but no significant differences were observed between either the NF and LI groups or the WMHI and LI groups (Table 1).

Correlation between total WMHI score and various factors was studied only for participants in the WMHI group. In this analysis, total WMHI was significantly correlated only with age at initial onset of depression ($r = 0.351$, $P < 0.05$) and age at time of interview ($r = 0.355$, $P < 0.05$), and no significant correlations were observed with systolic blood pressure. No diastolic blood pressure, history of hypertension, total cholesterol, triglycerides, lifetime smoking, lifetime alcohol consumption, and HRSD score (Table 1).

Survival analysis regarding achievement of remission during the study was carried out, but no significant differences were discovered among the three groups (Fig. 1). Figure 1 suggests that after less than 40 weeks all patients had fulfilled criteria for remission. However, dropout rates were high: 31.3%, 23.5% and 29.6% for the WMHI, LI, and NF groups, respectively. The proportionality of risk assumption for the survival curves was upheld ($\chi^2 = 0.486$, $P = 0.78$).

Three patients in the LI group were died by suicide between October 28, 1998 and January 31, 2003. There were no the suicide in the other group. Thus, the rate in the LI group was significantly higher than in the other groups (NF group + WMHI group) ($P = 0.0071$, Fisher exact test).

Discussion

In the current study, we observed no significant differences between the WMHI and NF groups regarding systolic blood pressure, diastolic blood pressure, or any other known risk factor for cerebrovascular disease. We also observed no significant correlations in the WMHI group between total WMHI and systolic blood pressure, diastolic blood pressure, or other known risk factors for cerebrovascular disease. Conversely, there were significant differences in systolic

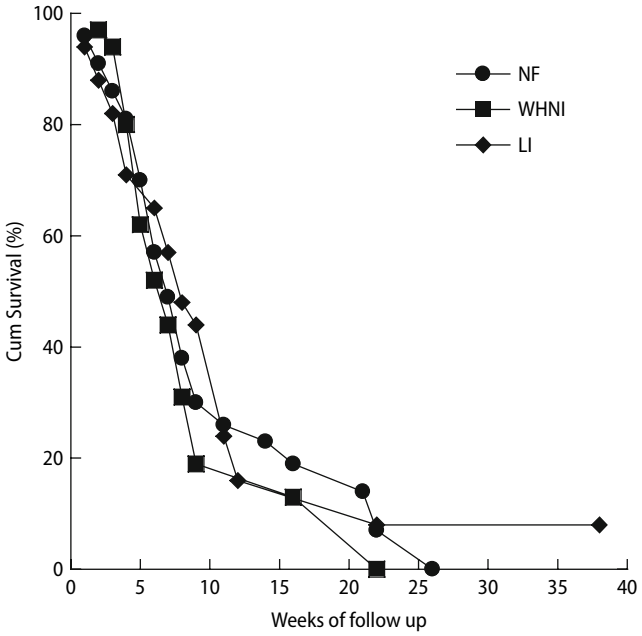

Fig. 1 Decline in proportion of patients who did not achieve remission by Kaplan–Meier survival curve

blood pressure and diastolic blood pressure between the WMHI and LI groups and between the NF and LI groups. These results suggest that hypertension is strongly related to LI but there is no direct relationship to WMHI. However, Greenwald et al. [8, 9] reported that WMHI was more intense in patients with depression and hypertension than in patients with depression and normal blood pressure, and that a relationship existed between WMHI and hypertension and WMHI and other risk factors for cerebrovascular disease. Differences in results between their research and ours may derive from differences in methodology. In the current study, we used an eligibility scheme that strictly excluded individuals with LI from the WMHI group.

Age at initial onset of depression was significantly higher in both the WMHI and LI groups than in the NF group, with no significant difference observed between the WMHI and LI groups. Age at time of interview demonstrated significant differences among all three groups, with the highest value in the LI group, followed by the WMHI group and the NF group. These results concur with results reported to date [3, 6, 9, 10]. Ylikoski et al. [21] reported that mild WMHI in elderly subjects without neurological disease were strongly related to age and also to the existence of associated silent infarct, atrophy, and some vascular risk factors, such as diabetes and cardiac arrhythmia. Longstreth et al. [17] found that greater age, clinically silent stroke on MRI, and higher systolic blood pressure correlated with WMHI lesions in patients without a history of stroke or transient ischemic attack. Schmidt et al. [13] suggested that clinically normal volunteers with WMHI were significantly older and more likely to have cardiac disease but had lower serum concentrations of total cholesterol than volunteers' subjects without WMHI.

Taken together, these results provide no evidence that cerebrovascular disease is related directly to formation of WMHI, suggesting instead that aging itself is an important risk factor for WMHI, and that WMHI contributes to onset of depression in the form of some organic factor. WMH is related to blood pressure and other cerebrovascular risk factors., incidence of cerebrovascular disease is related to aging. The age of at initial onset NF group was younger than one of WMHI and LI groups in our data. The difference of ages might influence the results.

The fact that the HRSD score was significantly higher in the WMHI group than in the NF group suggests that the severity of illness was greater in the WMHI group.

On average, there were no observed differences among the three patients groups in terms of response to treatment, but the fact that suicide occurred in the LI group suggests these patients have a poorer outcome. The current study has limitations. Antidepressants treatment was performed with a variety of antidepressants and medications were switched after only 4 weeks of non-response. We measured some risk factors for cerebrovascular disease such as smoking and total cholesterol and triglyceride levels. However, we did not measure a series of other significant risk factors including diabetes, obesity, sedentary lifestyle, antiphospholipid antibodies, low levels of vitamin B6, B12, and folate, carotid artery stenosis, and atrial fibrillation. The presence of WMHI was evaluated using a conventional scoring procedure by a single radiologist. Ideally, scoring should be done by two radiologists so any inter-observer differences can be identified. A weakness of the study is the high-dropout rate. The dropout was concentrated in the latter half of the study period. Because many patients were outpatients, there is a possibility that they gave up the treatment in this course by treatment if there was not improvement. However, the correlations with the age in onset and age of examination derived by discriminant function analyses (the NF, WMHI and LI groups) were significant. As age of examination was significantly different and the elder subjects had a higher probability for a later onset of depression, the individual age in onset and age of examination might influence the present study.

In conclusion, our findings suggest that the NF, WMHI, and LI groups have different, distinctive characteristics. Compared with control patients (the NF group), the WMHI group had higher ages at initial onset of depression and time of interview, in addition, the severity of their depression was greater. However, comparison of the same two groups revealed, no significant differences in systolic or diastolic blood

pressure, risk factors for cerebrovascular disease, family history of mood disorder, number of episodes or total days of prior depression, or occurrence of melancholic-features. When compared with the LI group, the WMHI group had a lower age at time of interview and lower systolic and diastolic blood pressures; however no differences were observed in age at initial onset of depression, risk factors for cerebrovascular disease, family history of mood disorder, number of episodes or total days of prior depression, occurrence of melancholic features, or severity of depression. The results regarding suicide suggest suicide that outcomes were worse in the LI group than in the other two groups.

Further research on patients with depression and WMHI is needed with study designs that strictly distinguish individuals with and without LI.

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