

Original Research Article

# Relationship between White Matter Lesions and Progression of Cognitive Decline in Alzheimer's Disease

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## Key Words

Alzheimer's disease · MRI · White matter lesions · Acetylcholinesterase inhibitor ·  
Rate of cognitive decline

## Abstract

**Background:** This study examined the relationship between baseline white matter lesions (WMLs) and the progression of cognitive decline in patients with late-onset Alzheimer's disease (AD). **Methods:** Fifty-six patients with AD were included in the study (23 men, 33 women; mean age, 77.8 years). All subjects were treated with acetylcholinesterase inhibitors and followed up for approximately 1 year. The Mini-Mental State Examination (MMSE) score was assessed at least twice to evaluate the progressive cognitive impairment. All subjects underwent brain MRI at baseline and were divided into WMLs(–), mild WMLs(+), and moderate WMLs(+) groups based on WML severity. Changes in MMSE scores between baseline and follow-up were analyzed using the Wilcoxon signed-rank test. **Results:** MMSE scores at baseline did not differ significantly among the three groups ( $p = 0.1658$ ), whereas MMSE scores at the follow-up evaluation were significantly lower in the moderate WMLs(+) group than in the WMLs(–) group ( $p = 0.0257$ ). The mean MMSE scores remained above baseline values during the approximately 1-year follow-up in the WMLs(–) group, whereas they were decreased in the mild and moderate WMLs(+) groups. Moreover, the frequency of improvement in patients from the WMLs(–) group tended to be higher than that in patients from the WMLs(+) groups. **Conclusion:** Baseline WMLs may be associated with the heterogeneous progression of cognitive decline in patients with AD.

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## Introduction

White matter lesions (WMLs) are commonly observed on T2-weighted MRI in healthy elderly people and patients with Alzheimer's disease (AD) and are distributed in the periventricular white matter and deep white matter [1–3]. Previous studies investigating the relationship between WMLs and cognitive impairment in patients with AD have reported conflicting results. Some studies have shown a significant relationship between WMLs and global cognitive function or neuropsychological performance, whereas others have failed to find any such relationships [3–6]. Therefore, we have previously used brain perfusion SPECT to objectively evaluate the effect of WMLs on brain function in patients with AD [7]. We found that regional cerebral blood flow was significantly decreased in the limbic system in AD patients with WMLs compared to those without WMLs. These findings led us to hypothesize that baseline WMLs influence the progression of cognitive decline in patients with AD. The role of WMLs as a predictor of clinical cognitive outcome has been demonstrated in healthy elderly individuals [8–10]. Few studies, however, have examined the relationship between baseline WMLs and the rate of future cognitive decline in patients with AD [11, 12]. For optimal diagnosis and treatment, it is important to determine the factors associated with disease progression. The aim of the present study was to evaluate the relationship between baseline WMLs and the progression of cognitive decline in AD patients treated with acetylcholinesterase inhibitors (AChE-I).

## Subjects and Methods

### *Subjects*

The subjects were selected among outpatients with late-onset (onset at the age of 65 years or after) and mild-to-moderate stage AD [11–24 points in the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating score 1 or 2] attending the Department of Neurology and Neuromuscular Disorders, Oita University Hospital, Oita, Japan, between 2006 and 2011 [7]. We excluded patients with a history of stroke or cerebral infarction and diffuse and extensive white matter changes on brain MRI. Other exclusion criteria, clinical evaluation, and routine laboratory tests were described elsewhere [7]. All subjects in the present study underwent MRI as a routine diagnostic procedure at baseline and were followed up for approximately 1 year after AChE-I therapy. Therefore, a total of 56 patients were included in this study (23 men, 33 women; mean age, 77.8 years). These patients received donepezil (5 mg/day), and the dose was increased to 10 mg/day in 14 patients over the 1-year study period because of progressive cognitive impairment. Moreover, 2 patients received memantine in addition to donepezil. The MMSE score was assessed at least twice during the present study to evaluate the progressive cognitive impairment. Information regarding age, sex, education level, neurological findings, and MMSE score at baseline and at the follow-up time point was extracted from the patients' medical records. Informed consent was obtained from the patients or relatives.

### *Brain MRI*

All patients were examined using T1-weighted, T2-weighted, and FLAIR images on a 1.5-tesla scanner (Excelart Vantage; Toshiba Medical System Corp., Tokyo, Japan). Briefly, white matter hyperintensities were classified as periventricular hyperintensities or deep white matter hyperintensities and graded from 0 to 3 using the Fazekas scale (0 indicates absent and 3 severe) [2], according to a previous study [7]. Patients with grade 3 (diffuse and extensive white matter changes) on the Fazekas scale were excluded because of the possi-

**Table 1.** Summary of clinical and demographic characteristics of the WMLs(-), mild WMLs(+), and moderate WMLs(+) groups

	WMLs(-) (n = 27)	Mild WMLs(+) (n = 17)	Moderate WMLs(+) (n = 12)	p value
Age, years	76.9±5.5	77.6±6.0	80.1±6.1	0.26
Sex (M/F)	10/17	9/8	4/8	0.23
Disease duration, years	1.6±1.0	2.0±1.4	2.1±1.0	0.41
Education, years	10.1±2.8	10.2±3.0	11.7±3.4	0.41
Treatment duration, months	12.3±1.1	12.9±1.7	12.3±1.0	0.58
MMSE score at baseline	20.2±3.8	17.9±4.8	18.3±5.4	0.17
MMSE score after treatment	20.4±5.5	16.8±6.5	16.5±4.4*	0.05

Values represent mean ± SD, unless otherwise indicated.

\* p < 0.05 was considered statistically significant.

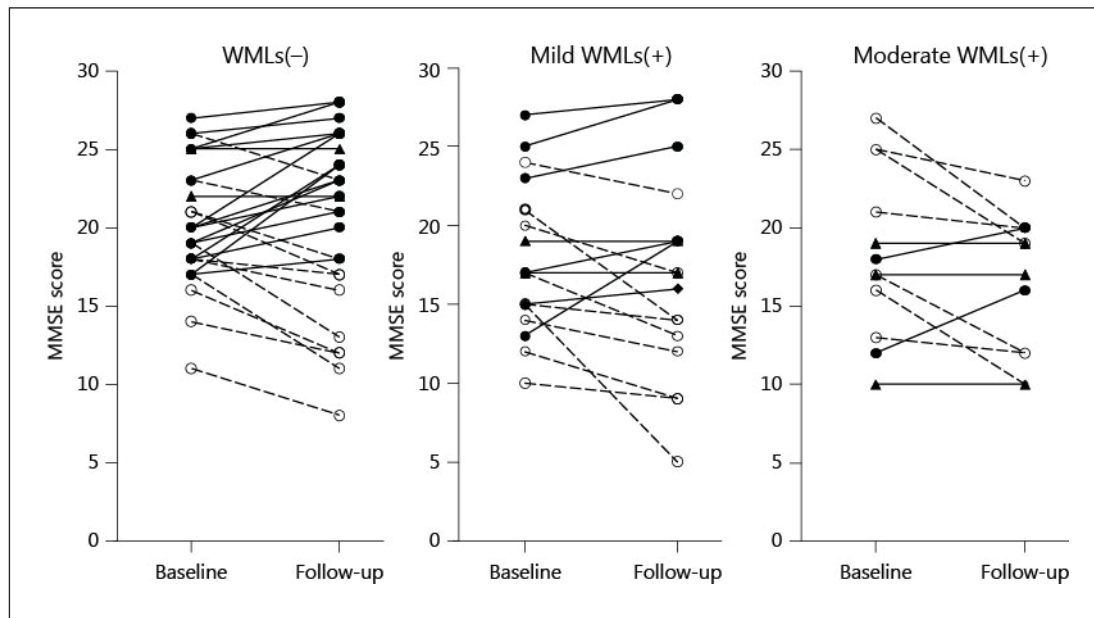
bility of vascular dementia. All images were retrospectively reviewed by two registered neurologists blinded to the medical information. In cases of disagreement, they reviewed the images again together to reach a consensus. All patients were divided into three subgroups based on the severity of their WMLs at baseline as follows: WMLs(-) group, grade 0 on the Fazekas scale for both periventricular and deep white matter; mild WMLs(+) group, grade 1 on the Fazekas scale for periventricular and/or deep white matter hyperintensities, and moderate WMLs(+) group, grade 2 on the Fazekas scale for periventricular and/or deep white matter hyperintensities. If the grades on the Fazekas scale were different between the periventricular and deep white matter, the more severe grade was used for analysis.

### Statistical Analysis

Between-group comparisons across the three subgroups were performed with a  $\chi^2$  test for sex distribution and a Kruskal-Wallis test for age at examination, sex distribution, disease duration, education level, treatment duration, and MMSE score. Changes in the MMSE score between baseline and follow-up were analyzed using the Wilcoxon signed-rank test. Moreover, all patients were divided into three subgroups: improved, stable, and declined based on the change in the MMSE score. The frequency of each clinical course was analyzed using a  $\chi^2$  test. A p value of less than 0.05 was considered statistically significant.

## Results

Table 1 summarizes the clinical and demographic characteristics of the WMLs(-), mild WMLs(+), and moderate WMLs(+) groups. The frequency of WMLs, such as periventricular or deep WMLs, was 52% (29/56); 17 patients had mild and 12 patients had moderate WMLs. There were no significant differences among the three subgroups in age at examination, sex distribution, disease duration, education level, or treatment duration. None of the patients showed focal neurological symptoms and signs due to cerebrovascular disease during the present study. MMSE scores at baseline did not differ significantly among the three subgroups (p = 0.17), whereas MMSE scores at the follow-up evaluation were significantly lower in the moderate WMLs(+) group than in the WMLs(-) group (p = 0.03). The comparison of MMSE scores at baseline and follow-up is shown in figure 1. The mean MMSE scores remained above baseline values during the approximately 1-year follow-up in the WMLs(-) group



**Fig. 1.** Comparison of MMSE scores between baseline and follow-up in the WMLs(-), mild WMLs(+), and moderate WMLs(+) groups. Among AD patients without WMLs, MMSE scores improved in 14, declined in 11, and did not change in 2 patients. Among the 17 patients with mild WMLs, MMSE scores increased in 6 (35%), decreased in 9 (53%), and did not change in 2 patients (12%). Among the 12 patients with moderate WMLs, MMSE scores increased in 2 (17%), decreased in 7 (58%), and did not change in 3 patients (25%). The mean MMSE scores remained above baseline values during the approximately 1-year follow-up in the WMLs(-) group (from  $20.2 \pm 3.8$  to  $20.4 \pm 5.5$ ,  $p = 0.84$ ), whereas they decreased in the mild WMLs(+) group from  $17.9 \pm 4.8$  to  $16.8 \pm 6.5$  ( $p = 0.29$ ) as well as in the moderate WMLs(+) group from  $18.3 \pm 5.4$  to  $16.5 \pm 4.4$  ( $p = 0.09$ ). ● = Patients with increased MMSE scores; ○ = patients with decreased MMSE scores; ▲ = patients with stable MMSE scores.

(from  $20.2 \pm 3.8$  to  $20.4 \pm 5.5$ ,  $p = 0.84$ , Wilcoxon signed-rank test), whereas they decreased in the mild WMLs(+) group from  $17.9 \pm 4.8$  to  $16.8 \pm 6.5$  ( $p = 0.29$ ) and in the moderate WMLs(+) group from  $18.3 \pm 5.4$  to  $16.5 \pm 4.4$  ( $p = 0.09$ ). Among the 27 patients without WMLs, MMSE scores increased in 14 (52%), decreased in 11 (41%), and did not change in 2 patients (7%). Among the 17 patients with mild WMLs, MMSE scores increased in 6 (35%), decreased in 9 (53%), and did not change in 2 patients (12%). Among the 12 patients with moderate WMLs, MMSE scores increased in 2 (17%), decreased in 7 (58%), and did not change in 3 patients (25%). The frequency of improved cognitive decline tended to be higher in the WMLs(-) group than in the mild and moderate WMLs(+) groups, but the difference was not statistically significant.

## Discussion

The findings of the present study show differences in the rate of cognitive decline between AD patients with and without WMLs. The mean MMSE scores of all patients decreased slightly from  $19.1 \pm 4.6$  to  $18.5 \pm 5.9$  during the approximately 1-year follow-up. A meta-analysis of the literature revealed that untreated AD patients lose at least 2.9 points on the MMSE per year [13]. Therefore, AChE-I was effective against progressive cognitive impairment

in our patients as a whole. The changes in the mean MMSE scores, however, differed between AD patients with and without WMLs. The mean MMSE scores remained above baseline values in the WMLs(-) group, whereas they decreased in the mild and moderate WMLs(+) groups. Moreover, the improvement tended to be higher in the WMLs(-) group than in the mild and moderate WMLs(+) groups. AD patients with WMLs showed a faster rate of change in MMSE scores during AChE-I treatment. These findings are consistent with those of previous studies suggesting baseline WMLs are associated with a more rapid cognitive decline in AD patients [11, 12]. Although the clinical response to AChE-I therapy and the rate of cognitive decline are considerably variable [14, 15], the reasons for this remain unclear. We suggest that baseline WMLs might be associated with the heterogeneous cognitive outcome and response to AChE-I in AD patients.

Neuropathological studies showed that AD patients with vascular lesions have less AD pathology, including neuritic plaques and neurofibrillary tangles, compared to those without vascular pathology, despite the same severity of cognitive impairment [16]. Moreover, cerebrovascular disease may promote A $\beta$  aggregation or plaque formation and cognitive decline in early or mild AD [17, 18]. These findings suggest that AD pathology and small vessel disease act synergistically in the course of cognitive symptoms in AD [13]. Moreover, neuroimaging data revealed a relationship between WMLs and regional cerebral blood flow or cerebral metabolism in AD patients. AD patients with WMLs have decreased metabolism in the frontal lobes on positron emission tomography and hypoperfusion in the hippocampal regions on brain perfusion SPECT [19, 20]. Similarly, we previously reported that AD patients with WMLs showed hypoperfusion in the limbic system compared to those without WMLs [7]. These findings suggest that WMLs contribute to the decreased brain function in AD patients. Therefore, we propose that WMLs influence the progression of cognitive decline through neuropathological and brain functional mechanisms. Future studies are needed to investigate the effects of preventing WMLs on the progression of cognitive decline in AD.

The present study has several limitations. First, we selected late-onset AD patients with mild-to-moderate dementia because the severity of white matter involvement is associated with age and severity of cognitive impairment. Second, the dose of donepezil was 5 mg/day, which is lower than the international standard (10 mg/day). In Japan, donepezil at a dose of 5 mg/day is indicated for mild-to-moderate AD [21]. Third, the follow-up MRI study was not performed to assess cerebrovascular disease and progression of WMLs. Although the incidence of cerebrovascular disease could not be completely excluded, especially in the patients with rapid cognitive decline, none of the patients showed focal neurological symptoms and signs. Moreover, our results could not demonstrate a correlation between the progression of WMLs and the rate of cognitive decline.

In conclusion, the present study reveals a difference in the rate of cognitive decline between AD patients with and without baseline WMLs. We suggest that baseline WMLs may be associated with a more rapid cognitive decline and the response to AChE-I in AD patients.

### Disclosure Statement

The authors have no conflicts of interest to declare.



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