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Original Research Article

Frontal White Matter Hyperintensity Is Associated with Verbal Aggressiveness in Elderly Women with Alzheimer Disease and Amnestic Mild Cognitive Impairment

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Keywords

Aggression · Alzheimer disease · Mild cognitive impairment · Behavioral and psychological symptoms in dementia · White matter hyperintensities

Abstract

Background/Aims: Behavioral and psychological symptoms of dementia (BPSD) are exhibited in most patients with Alzheimer disease (AD). Although white matter hyperintensity (WMH) is often observed with AD, the precise role of WMH in BPSD remains unclear. The current study aimed to identify the impact of regional WMH on specific features of BPSD in persons with mild to moderate AD and amnestic mild cognitive impairment (aMCI). ***Methods:*** A sample of 256 female outpatients with AD (n = 217) and aMCI (n = 39) were recruited. We assessed BPSD using the Dementia Behavior Disturbance Scale. WMH and brain atrophy were evaluated using an automatic segmentation program. Regional WMH was evaluated as periventricular hyperintensity (PVH) and deep WMH in frontal, temporal, occipital, and parietal lobes. ***Results:*** Whole-brain WMH was associated with verbal aggressiveness. In multivariate analysis, PVH in the frontal lobe was independently associated with verbal aggressiveness after adjustment for brain atrophy and clinical confounders. ***Conclusion:*** The current results indicated that PVH in the frontal lobe was independently associated with verbal aggressiveness.

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Introduction

Behavioral and psychological symptoms of dementia (BPSD) are used to describe a heterogeneous group of noncognitive symptoms, defined as signs and symptoms of disturbed perception, thought content, mood, or behavior [1]. BPSD are observed in nearly all persons with dementia during the course of illness [2]. Furthermore, BPSD are exhibited in approximately half of patients with mild cognitive impairment (MCI) [3]. BPSD are associated with poor outcomes, including reduced quality of life [4], increased caregiver burden [5], conversion from MCI to dementia [6], and progression to severe dementia and/or death [7]. Therefore, identifying the factors associated with BPSD and developing preventive strategies could be valuable in persons with MCI and the early stages of dementia.

White matter hyperintensity (WMH) is presumed to be of vascular origin and is commonly used as a marker of cerebrovascular disease. WMH is considered to coexist with Alzheimer disease (AD) pathologies [8], patients with AD have been found to exhibit a greater WMH volume, and amnestic MCI (aMCI) patients exhibit an intermediate level of WMH between that of AD patients and healthy controls with normal cognition [9]. Confluent and extensive WMH is associated with not only cognitive impairment, but also mobility dysfunction and functional decline [8–13]. Several previous imaging studies have examined the association between WMH and BPSD [10, 14–18]. However, these studies have reported inconsistent results. While one study found that patients with WMH were more likely to exhibit BPSD [17], another study did not find any association [15]. Several studies have examined the association between WMH and specific patterns of BPSD, but their results are also inconsistent [10, 14–16]. These inconsistencies may be explained by differences in WMH rating scales. Importantly, the regional impact of WMH on specific patterns of BPSD has not been considered. In addition, expression and BPSD features vary according to the clinical course of dementia [2], and many factors, including gender, cognitive impairment, medical health, medication, and environmental factors, are also known to influence the occurrence of BPSD [19, 20].

Considering these issues, the current study sought to clarify the relationship between a volumetric assessment of WMH and BPSD in early AD and aMCI. We hypothesized that regional WMH would be independently associated with specific features of BPSD. Thus, the aim of this study was to determine the regional effects of WMH on specific features of BPSD after adjusting for brain atrophy and clinical confounders.

Methods

Participants

This study obtained ethical approval from the National Center for Geriatrics and Gerontology (NCGG). All candidate patients and their caregivers provided written informed consent before participating in the study. We enrolled 256 outpatients who visited the NCGG hospital between 2010 and 2013 with a diagnosis of probable or possible AD (n = 217) or aMCI (n = 39) based on the criteria of the National Institute on Aging/Alzheimer's Association Workgroup [21, 22]. Because the prevalence of BPSD is dependent on gender [19], this study included only female patients. All subjects were aged 65–85 years and had Mini-Mental State Examination (MMSE) scores ≥15 and Barthel Index scores ≥80. Patients with delirium, a history of stroke or cortical lesions detected on magnetic resonance (MR) images, severe conditions, such as cardiac failure, renal disorder, or liver dysfunction, or neurological disorders other than AD were excluded from the study.

Assessment of BPSD and Clinical Confounding Factors

We used clinical data collection in the NCGG Medical Genome Center Biobank, which stores bioresources and clinical data for biomedical research. BPSD was evaluated using the Dementia Behavior Disturbance Scale (DBD) [23]. Patients' caregivers were surveyed and rated the occurrence of particular behaviors on a scale from 0 to 4 points (0, never; 1, rarely; 2, sometimes; 3, often; 4, all the time). In our previous study of a large cohort of patients with AD, factor analysis was carried out on 28 sub-items of the DBD; the DBD was classified into 6 domains [5]. The domain "incontinence," included in the scale, identifies the relevance of regional WMH [24]. Therefore, the current study examined the following 5 domains: behavioral disturbance (e.g., wandering, getting lost outside), verbal aggressiveness (e.g., accusations, verbal abusiveness), motor aggressiveness (e.g., physical attacks, destroys property or clothing), memory impairment (e.g., asking the same question repeatedly, losing, misplacing, or hiding things), and apathy (e.g., lack of interest in daily activities, sleeping excessively during the day).

Global cognition was assessed with the MMSE [25]. Basic/instrumental activities of daily living were assessed with the Barthel Index and Lawton Index, respectively [26, 27]. Depressive mood was evaluated with the self-rated Geriatric Depression Scale-15 (GDS) and Vitality Index, respectively [28, 29]. Geriatric syndrome was evaluated with the following items: lower urinary tract symptoms (urinary incontinence, urinary difficulty, and urinary frequency), pain (lumbago, back pain, leg and upper limb pain), fatigue, constipation/diarrhea, and sleep problems. We assessed polypharmacy and the following medications: use of donepezil, memantine hydrochloride, antipsychotics, and anti-anxiety/sleeping medicines. Polypharmacy was defined as taking 5 or more types of oral medicine [30]. The patients' lifestyle factors and social conditions were assessed using the following questions: participation in social activity (yes or no), exercise (none, once or more per week), need for financial support (yes or no), alcohol consumption (daily or none), current smoking status (yes or no), and living situation (with parents or children, spouse, alone or other). In cases where patients lived alone, we obtained DBD information from the patient's family, who provided as much information as they could about the patient's behaviors. If the patient's family could not answer all questions about the patient's behavior, the case was excluded from the study.

Evaluation of WMH and Brain Atrophy

Image acquisition parameters of MR imaging and methodological details were the same as those described in our previous study [24]. Briefly, all participants underwent 1.5-T brain MR imaging (Siemens Avanto, Germany; or Philips Ingenia, The Netherlands) with T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequence. WMH and brain atrophy were quantified using an automatic segmentation application (SNIPER, Software for Neuro-Image Processing in Experimental Research, Department of Radiology, Leiden University Medical Center, The Netherlands) [31]. Brain tissue was classified as frontal, temporal, occipital, and parietal lobes, and WMH was separated into periventricular hyperintensity (PVH) and deep WMH (DWMH). Because automatic segmentation of WMH mostly recognized DWMH in continuity with PVH, the distinction was manually classified [32]. Global brain atrophy was assessed by parenchyma, which is the subtraction of cerebrospinal fluid from intracranial (IC) volume, corresponding to the sum of total gray and white matter volumes. To minimize the bias of individual brain size, total and regional WMH and parenchyma were divided by the IC volume.

Statistical Analysis

All data were analyzed using the Japanese version of SPSS for Windows version 22.0 (IBM Corporation, Armonk, NY, USA). First, we performed multiple regression analyses to

identify the association between MR imaging parameters and DBD subcategories. Second, to explore potential risk factors for BPSD, we performed single regression analysis. We calculated the coefficient of determination for each clinical index to determine the association with DBD subcategories. Finally, to identify the independent risk factors for BPSD, we conducted 2 sets of multiple regression analyses. Dependent variables were DBD subcategories and sub-items. Age, education, regional WMH, brain atrophy, and classical confounders known to influence development of BPSD (i.e., global cognitive function, geriatric syndrome, medication, and social activity [20]) were entered as independent variables in model 1. Age, education, regional WMH, brain atrophy, classical confounders, and clinical indices showing an association with DBD subcategories were entered as independent variables in model 2. Variance inflation factors were calculated for all multiple regression models and indicated no violation of linearity and multicollinearity. The level of statistical significance was set at $p < 0.05$.

Results

Clinical Data

The clinical profiles of the study participants are shown in Table 1. The mean age was 77.3 ± 5.2 years, and the total MMSE score was 21.2 ± 3.7. The total DBD score was 15.5 ± 10.6. In MR imaging analysis, mean IC volume and total WMH were 1,328.6 ± 98.3 mL and 17.0 ± 17.7 mL, respectively. Regional distribution of WMH exhibited a high prevalence in the frontal (9.5 ± 9.6 mL) and parietal lobes (5.8 ± 7.0 mL) compared to other regions. Because automatic segmentation recognizes WMH as 3-D continuity in each MR imaging slice [32], most WMH was recognized as PVH (16.0 ± 17.3 mL), and there was markedly less DWMH (1.0 ± 1.3 mL).

Associations between MR Imaging Parameters and BPSD Subdomains

The associations between WMH and brain atrophy with DBD subcategories are shown in Table 2. After adjustment for age and education, total WMH was associated with verbal aggressiveness. In the regional analysis, PVH in the frontal lobe was associated with verbal aggressiveness. However, other regional PVH and DWMH were not associated with DBD subcategories. Brain atrophy was not associated with any DBD subcategories.

Association between Clinical Parameters and Verbal Aggressiveness

To explore the clinical confounders for verbal aggressiveness, we performed single regression analysis and calculated coefficients of determination (Table 3). The results revealed that verbal aggressiveness was significantly associated with fewer years of education, lower MMSE scores, decline of basic/instrumental activities of daily living, low vitality, number of geriatric syndromes, and fatigue. Regarding medications, verbal aggressiveness was significantly associated with treatment with antipsychotics, but other medications, including the dosage of donepezil, were not associated with verbal aggressiveness. None of the indices of lifestyle and social conditions, such as living situation, were associated with verbal aggressiveness.

Independent Risk Factors for Verbal Aggressiveness

Finally, to explore independent risk factors for verbal aggressiveness, we conducted 2 sets of multiple regression analyses (Table 4). The domain of verbal aggressiveness included the following 4 sub-items: "makes unwarranted accusations," "verbally abusive, swears," "cries or laughs inappropriately," and "screams for no reason" [5]. Therefore, we examined the relationship between regional WMH and verbal aggressiveness including these sub-items.

Table 1. Clinical characteristics of study participants (n = 256)

Age, years	77.3±5.2	
Education, years	10.1±2.0	
Mini-Mental State Examination	21.1±3.7	
Barthel Index	98.5±3.8	
Lawton Index	6.1±1.7	
Geriatric Depression Scale	4.3±2.6	
Vitality Index	9.1±1.1	
Dementia Behavior Disturbance Scale	15.5±10.6	
Geriatric syndromes		
Number of geriatric syndromes	1.6±1.3	
Lower urinary tract symptoms	85 (33.2)	
Pain	146 (57.0)	
Fatigue	69 (27.0)	
Constipation or diarrhea	61 (23.8)	
Sleep problems	44 (17.2)	
Medication		
Polypharmacy	119 (46.5)	
Donepezil	55 (21.5)	
Memantine hydrochloride	2 (0.8)	
Antipsychotics	26 (10.2)	
Anti-anxiety/sleeping medicine	66 (25.8)	
Lifestyle		
Social activity	83 (32.4)	
Exercise, once or more/week	174 (68.0)	
Finance, support needed	19 (7.4)	
Alcohol, daily drinking	19 (7.4)	
Current smoking	6 (2.3)	
Social condition		
Living with parents or children	122 (47.7)	
Living with spouse	85 (33.2)	
Living alone or other	49 (19.1)	
MR imaging analysis		
IC volume, mL	1,328.6±98.3	
PAR, mL	998.2±82.0	75.1%[a]
WMH total, mL	17.0±17.7	1.28%[a]
Frontal lobe, mL	9.5±9.6	0.72%[a]
Temporal lobe, mL	1.2±1.6	0.09%[a]
Occipital lobe, mL	0.5±0.7	0.04%[a]
Parietal lobe, mL	5.8±7.0	0.44%[a]
Periventricular area, mL	16.0±17.3	1.20%[a]
Deep subcortical areas, mL	1.0±1.3	0.08%[a]

Data are presented as means ± standard deviations or n (%) unless otherwise indicated. IC, intracranial; MR, magnetic resonance; PAR, parenchyma; WMH, white matter hyperintensity. [a] % of IC volume.

In model 1, age, education, PVH in the frontal lobe, brain atrophy, and classical confounders were entered as independent variables. The results revealed that PVH in the frontal lobe was independently associated with the category of verbal aggressiveness and the sub-items "makes unwarranted accusations" and "verbally abusive, swears." However, PVH in the frontal lobe was not associated with "cries or laughs inappropriately" or "screams for no reason" (β = 0.02, p = 0.730 and β = 0.02, p = 0.731, respectively). These 2 sub-items were only

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Table 2. Associations between WMH and brain atrophy with DBD subcategories

	Behavioral disturbance (n = 54)			Verbal aggressiveness (n = 75)			Motor aggressiveness (n = 6)			Memory impairment (n = 246)			Apathy (n = 151)		
	β	95% CI	p value	β	95% CI	p value	β	95% CI	p value	β	95% CI	p value	β	95% CI	p value
Total WMH	0.07	(−0.10; 0.38)	0.266	0.19	(0.11; 0.58)	0.004	−0.01	(−0.09; 0.07)	0.853	−0.01	(−0.28; 0.25)	0.927	0.05	(−0.12; 0.26)	0.450
PAR	0.07	(−0.05; 0.16)	0.289	−0.02	(−0.12; 0.09)	0.812	0.03	(−0.03; 0.05)	0.658	−0.02	(−0.14; 0.10)	0.750	−0.07	(−0.13; 0.04)	0.273
PVH in frontal lobe	0.20	(−0.15; 1.51)	0.108	0.25	(0.03; 1.64)	0.043	−0.01	(−0.29; 0.28)	0.951	0.10	(−0.54; 1.30)	0.418	0.19	(−0.15; 1.17)	0.132
PVH in temporal lobe	−0.03	(−5.73; 4.52)	0.816	−0.14	(−7.80; 2.15)	0.265	−0.22	(−3.30; 0.20)	0.082	−0.05	(−6.74; 4.61)	0.711	0.11	(−2.31; 5.84)	0.393
PVH in occipital lobe	−0.01	(−9.09; 7.83)	0.884	0.10	(−3.67; 12.75)	0.278	0.12	(−1.14; 4.63)	0.235	0.08	(−5.26; 13.47)	0.389	−0.11	(−10.76; 2.69)	0.238
PVH in parietal lobe	−0.08	(−1.89; 1.12)	0.617	0.00	(−1.47; 1.46)	0.992	0.09	(−0.37; 0.66)	0.580	−0.12	(−2.27; 1.06)	0.477	−0.13	(−1.69; 0.71)	0.419
PAR	0.08	(−0.04; 0.17)	0.237	0.00	(−0.10; 0.11)	0.995	0.05	(−0.02; 0.05)	0.507	−0.02	(−0.13; 0.10)	0.804	−0.08	(−0.13; 0.04)	0.276

Multiple regression analysis with forced entry method. We conducted 2 analyses to examine the association between total WMH, regional WMH and DBD subcategories. All analyses were adjusted for age and education. The dependent variables were DBD subcategories that summed the scores of the sub-items of each subcategory. The presence of each symptom was defined as a score of 2–4 points (2, sometimes; 3, often; 4, all the time) of at least 1 or more sub-items. CI, confidence interval; DBD, Dementia Behavior Disturbance Scale; PAR, parenchyma; PVH, periventricular hyperintensity; WMH, white matter hyperintensity.

Table 3. Associations between clinical parameters and verbal aggressiveness

	Verbal aggressiveness		
	β	95% CI	R^2
Age	0.03	(−0.04; 0.07)	0.001
Education	−0.13	(−0.30; −0.01)	0.017
Mini-Mental State Examination	−0.16	(−0.18; −0.02)	0.025
Activity of daily living			
Barthel Index	−0.18	(−0.19; −0.03)	0.031
Lawton Index	−0.27	(−0.53; −0.20)	0.070
Mood disturbance			
Geriatric Depression Scale	0.08	(−0.04; 0.18)	0.006
Vitality Index	−0.19	(−0.66; −0.14)	0.034
Geriatric syndromes			
Number of geriatric syndromes	0.22	(0.18; 0.62)	0.047
Lower urinary tract symptoms	0.12	(−0.03; 1.21)	0.014
Pain	0.07	(−0.27; 0.92)	0.005
Fatigue	0.24	(0.65; 1.93)	0.058
Constipation or diarrhea	0.11	(−0.09; 1.29)	0.011
Sleep problems	0.11	(−0.09; 1.46)	0.012
Medication			
Polypharmacy	0.10	(−0.10; 1.07)	0.010
Donepezil	0.09	(−0.22; 1.21)	0.007
Memantine hydrochloride	0.03	(−2.44; 4.26)	0.001
Antipsychotics	0.17	(0.37; 2.28)	0.029
Anti-anxiety/sleeping medicine	0.02	(−0.57; 0.77)	0.000

Single regression analysis. The dependent variables were verbal aggressiveness of the DBD subcategory. R^2 is the proportion of explained variance of verbal aggressiveness. CI, confidence interval; DBD, Dementia Behavior Disturbance Scale.

associated with fewer years of education (β = −0.18, p = 0.009 for "cries or laughs inappropriately") and number of geriatric syndromes (β = 0.16, p = 0.019 for "screams for no reason").

In model 2, age, education, PVH in the frontal lobe, brain atrophy, classical confounders, and clinical indices showing an association with verbal aggressiveness were entered as independent variables. The results revealed that PVH in the frontal lobe was independently associated with the category of verbal aggressiveness and the sub-items "makes unwarranted accusations" and "verbally abusive, swears." In addition, treatment with antipsychotics was associated with the category of verbal aggressiveness and the 2 sub-items. Fewer years of education and fatigue were associated with the category of verbal aggressiveness and the sub-item "verbally abusive, swears." The number of geriatric syndromes was associated with "makes unwarranted accusations."

Discussion

The current study revealed that PVH in the frontal lobe was independently associated with verbal aggressiveness in female patients with mild to moderate AD or aMCI. This association remained significant even after multivariable adjustment, including brain atrophy, cognitive impairment, geriatric syndrome, medication, and environmental factors.

Table 4. Independent risk factors for verbal aggressiveness

	Verbal aggressiveness			Verbal aggressiveness sub-items					
				makes unwarranted accusations			verbally abusive, swears		
	β	95% CI	*p* value	β	95% CI	*p* value	β	95% CI	*p* value
Model 1									
Age	−0.11	(−0.12; 0.01)	0.122	−0.11	(−0.05; 0.01)	0.113	−0.08	(−0.04; 0.01)	0.277
Education	−0.17	(−0.35; −0.04)	0.012	−0.12	(−0.12; 0.01)	0.081	−0.15	(−0.14; −0.01)	0.028
PVH in frontal lobe	0.17	(0.14; 1.03)	0.011	0.24	(0.16; 0.54)	<0.001	0.14	(0.01; 0.39)	0.044
PAR	−0.02	(−0.12; 0.09)	0.778	−0.09	(−0.08; 0.02)	0.197	−0.01	(−0.05; 0.04)	0.939
Mini-Mental State Examination	−0.11	(−0.15; 0.01)	0.094	−0.12	(−0.07; 0.00)	0.054	−0.09	(−0.06; 0.01)	0.174
Number of geriatric syndromes	0.24	(0.20; 0.67)	<0.001	0.24	(0.09; 0.29)	<0.001	0.20	(0.06; 0.26)	0.002
Polypharmacy	0.00	(−0.59; 0.63)	0.946	0.00	(−0.27; 0.26)	0.955	0.05	(−0.15; 0.37)	0.409
Social activity	−0.07	(−0.97; 0.27)	0.263	−0.01	(−0.28; 0.26)	0.941	−0.10	(−0.48; 0.05)	0.110
Model 2									
Age	−0.13	(−0.12; 0.00)	0.063	−0.12	(−0.05; 0.00)	0.079	−0.10	(−0.05; 0.01)	0.169
Education	−0.17	(−0.34; −0.05)	0.009	−0.12	(−0.13; 0.00)	0.066	−0.15	(−0.14; −0.01)	0.017
PVH in frontal lobe	0.14	(0.05; 0.91)	0.028	0.22	(0.13; 0.51)	0.001	0.13	(0.00; 0.37)	0.048
PAR	−0.01	(−0.11; 0.10)	0.936	−0.08	(−0.07; 0.02)	0.238	−0.01	(−0.05; 0.04)	0.873
Mini-Mental State Examination	−0.06	(−0.12; 0.04)	0.343	−0.10	(−0.06; 0.01)	0.154		N/A	
Number of geriatric syndromes	0.11	(−0.07; 0.47)	0.140	0.16	(0.01; 0.24)	0.035	0.07	(−0.06; 0.17)	0.384
Polypharmacy		N/A			N/A			N/A	
Social activity		N/A			N/A			N/A	
Lawton Index	−0.12	(−0.37; 0.03)	0.099	−0.07	(−0.13; 0.05)	0.358	−0.09	(−0.14; 0.03)	0.224
Vitality Index	−0.08	(−0.47; 0.10)	0.206	−0.05	(−0.17; 0.08)	0.482	−0.12	(−0.23; 0.01)	0.080
Fatigue	0.16	(0.08; 1.63)	0.031	0.08	(−0.15; 0.53)	0.279	0.20	(0.11; 0.78)	0.009
Antipsychotics	0.14	(0.18; 1.99)	0.019	0.14	(0.08; 0.87)	0.020	0.13	(0.05; 0.83)	0.028

Multiple regression analysis with forced entry method. The dependent variables were verbal aggressiveness and sub-items. Model 1: age, education, PVH in the frontal lobe, PAR, and classical confounders (Mini-Mental State Examination, number of geriatric syndromes, polypharmacy, and social activity) were entered as independent variables. Model 2: age, education, PVH in the frontal lobe, PAR, and classical confounders ($p < 0.1$ in model 1) and clinical indices (Lawton Index, Vitality Index, fatigue, and antipsychotics, which exhibited the highest R^2 values in each clinical section in Table 3) were entered as independent variables. N/A indicates that the model was not conducted because classical confounders were $p > 0.1$ in model 1. CI, confidence interval; PAR, parenchyma; PVH, periventricular hyperintensity.

To date, several studies have examined the relationship between whole-brain WMH and BPSD [14–17], but their results were inconsistent. We first demonstrated that PVH in the frontal lobe was significantly associated with verbal aggressiveness. Aggression in dementia has been found to be related to neural networks in various brain regions, particularly in frontal areas [33, 34]. Several studies have reported that patients with aggression exhibit more atrophy in the frontal cortex and limbic regions, including the cingulate cortex, amygdala, and insula [35–37], and hypoperfusion in the frontotemporal cortex [38]. Furthermore, reduced white matter integrity in the anterior cingulum was significantly associated with irritability and a tendency to exhibit agitation [39]. Frontal regions have abundant connections with major projecting fibers, including the integration of limbic and emotional information into behavioral responses [40]. The participants in the current study exhibited relatively moderate to severe WMH volume (17.0 mL, 1.28% of IC volume), corresponding to grade 2–3 on the Fazekas scale [32]. In addition, most of the observed WMH was distributed in the periventricular region. Deep subcortical regions connect to adjacent areas via U-fibers, whereas the periventricular region contains long association fibers that connect to distant multiple brain areas. Therefore, the current observations indicated that frontal PVH disrupts neural pathways mainly in the frontal lobe and its associated networks, which may provoke verbal aggressiveness.

In contrast to our observations, several previous studies have reported no significant associations between WMH and aggression [14–16, 18]. Furthermore, one previous study

reported that aggression was more directly related to AD pathology than vascular lesions [41]. These discrepancies may be related to the heterogeneous methodologies used for the assessment of aggression and differences in the study populations. In the current study, we used the DBD for the assessment of BPSD, whereas most previous studies have used the neuropsychiatric inventory (NPI) [14–16, 18]. The NPI encompasses related subdomains, and the "agitation/aggression" domain includes physical aggression, verbal aggression, and resistance to care [42, 43]. Thus, even though patients exhibit different types of aggressive behaviors, they are included in the "agitation/aggression" domain. There was no association between WMH and motor aggressiveness in the current study, suggesting that the impact of WMH may vary for different types of aggression. A previous study showed that verbal aggression was significantly associated with lower cerebral blood flow in the left inferior frontal gyrus and the left insula, whereas physical aggression was significantly associated with the right superior temporal gyrus and the right inferior frontal gyrus [44]. Regarding the study population, the current study included only female patients with mild to moderate AD or aMCI. Female AD and aMCI patients have been shown to exhibit verbal aggressiveness more frequently, while male patients tend to exhibit more physical aggressiveness [19, 45]. Moreover, aggression typically increases with AD progression [46]. The participants in the current study were early AD and aMCI patients with preserved verbal abilities, possibly resulting in verbal aggressiveness occurring more often than motor aggressiveness. Moreover, the sub-items "cries or laughs inappropriately" and "screams for no reason," which do not require language ability, were not related to frontal PVH in the current study. Thus, frontal PVH may affect verbal aggressiveness during the period in which language ability is maintained. Because aggressiveness is reported to be predictive of rapid progression to severe dementia and earlier death [7], treating aggression in early AD or aMCI may have important benefits.

Previous studies indicated that WMH has a higher prevalence in AD patients, and aMCI patients exhibit an intermediate level of WMH between that of AD patients and persons with normal cognition [9]. Cerebral amyloid angiopathy (CAA) is often found in AD and is an important contributor to WMH formation [8, 47]. A recent imaging study by the Alzheimer's Disease Neuroimaging Initiative (ADNI) revealed a relationship between periventricular WMH and elevated cerebral amyloid [48]. Interestingly, a regional analysis in that study revealed that periventricular WMH in the frontal lobe was associated with elevated amyloid in subjects with normal cognition, whereas there was no significant association in MCI subjects. CAA is reported to be more predominant in posterior areas [49], and the distribution of WMH in patients with CAA has been predominantly observed in posterior regions [50, 51]. Conversely, a frontal predominance of WMH has been shown in normal elderly individuals and markedly increases with aging [52, 53]. Thus, the current results suggest that patients with AD may have predominantly exhibited posterior WMH, but the further addition of frontal WMH may be related to the specific features of BPSD. There is evidence that aging and hypertension are strong risk factors for WMH progression, but diabetes, dyslipidemia, inflammation, oxidative stress, and sleeping disorders are also associated with the acceleration of WMH [54]. Prevention and therapeutic intervention for these risk factors may be valuable for suppressing the progression of WMH, particularly in frontal regions.

Consistent with previous studies, geriatric syndrome and fatigue were significantly associated with verbal aggressiveness [20, 45, 55, 56]. Medical problems in older persons with dementia can cause discomfort and play a critical role in verbal aggressiveness [20, 45, 55]. Fatigue is one of the stressors underlying BPSD [57], and verbal aggressiveness is exacerbated by fatigue [56]. One previous study suggested that verbal aggressiveness can result from discomfort due to daytime fatigue caused by insufficient sleep [58]. In the current study,

participants with sleep problems exhibited more fatigue than those without sleep problems (50.0 vs. 22.2%, $p < 0.001$, χ^2 test). Thus, comprehensive treatment of geriatric syndromes, particularly fatigue, may reduce verbal aggressiveness in persons with dementia.

Use of antipsychotic medication was significantly associated with verbal aggressiveness. Although treatment with antipsychotics in the management of BPSD is controversial because of the risk of adverse effects, antipsychotics are commonly prescribed as a pharmacological treatment and can be effective for aggression [20]. In the current study, patients who were treated with antipsychotics had high scores for the sub-items "makes unwarranted accusations" (1.2 vs. 0.6, $p = 0.008$, unpaired t test) and "verbally abusive, swears" (1.1 vs. 0.6, $p = 0.010$, unpaired t test). Therefore, it is likely that antipsychotic treatment was an associated factor in the current study but may not be a risk factor for verbal aggressiveness.

The current study involved several limitations that should be considered. First, because the study design was cross-sectional, the potential causality between WMH and verbal aggressiveness should be considered cautiously. Second, because the DBD does not include psychotic domains, we could not examine the relationship between WMH and psychotic symptoms. One previous study reported that delusions were associated with frontal WMH [18]. Thus, further studies are required to clarify the precise role of regional WMH in psychotic symptoms. Finally, we were unable to analyze WMH by hemisphere. One previous study reported that verbal aggression was associated with lower regional cerebral blood flow in the left hemisphere, whereas physical aggression was associated with blood flow in the right hemisphere [44]. Future studies will be needed to evaluate WMH by hemisphere and clarify this issue further.

In conclusion, PVH in the frontal lobe was independently associated with verbal aggressiveness in female patients with mild to moderate AD and aMCI. In addition, geriatric syndromes, particularly fatigue, were also associated with verbal aggressiveness. Additional studies in the future would be valuable to provide further evidence to support the present findings and to develop preventive strategies against WMH progression.

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Disclosure Statement

The authors report no conflicts of interest.

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