Impact of regional white matter hyperintensities on specific gait function in Alzheimer's disease and mild cognitive impairment

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Abstract

Background   Gait disturbance and musculoskeletal changes are evident in persons living with Alzheimer's disease (AD). Because complex gait control requires the integration of neural networks, cerebral small vessel disease (SVD), which is highly prevalent in persons with AD, might have an additional impact on gait disturbance. This study investigated whether white matter hyperintensities (WMH) are more predominantly associated with gait disturbance in persons with AD than in individuals with mild cognitive impairment (MCI) and normal cognition (NC) and further identified the regional impact of WMH on specific gait changes.

Methods   This study included 396 subjects (aged 65 to 86 years, 63.9% female) diagnosed with AD ($n = 187$), MCI ($n = 118$), or NC ($n = 91$). WMH, lacunes, perivascular spaces, and cerebral microbleeds were assessed as markers of SVD. The volume of WMH was quantified in each brain lobe (frontal, temporal, occipital, and parietal) and sublobar regions in the basal ganglia and thalamus. Gait function was assessed using an electronic walkway. We investigated the association between regional WMH and gait disturbance in individuals with AD, MCI, and NC, adjusted for classical and musculoskeletal confounders.

Results   Among markers of SVD, WMH were most associated with gait disturbance. In AD subjects, periventricular WMH in the frontal and parietal lobes were associated with slow gait speed ($r_s = -0.21$, $P = 0.007$ and $r_s = -0.18$, $P = 0.019$, respectively). These lesions were also associated with changes in stride time, double-leg support time, and walking angle (all $r_s > 0.20$, $P < 0.01$). Lesions in the basal ganglia and thalamus were associated with slow gait speed ($r_s = -0.16$, $P = 0.034$ and $r_s = -0.18$, $P = 0.023$, respectively) and greater gait speed variability ($r_s = 0.16$, $P = 0.034$ and $r_s = 0.20$, $P = 0.010$, respectively). MCI subjects showed only associations between sublobar lesions and shorter stride length ($r_s = -0.24$, $P = 0.016$) and increased walking angle ($r_s = 0.32$, $P = 0.002$). NC subjects did not show associations between WMH and gait parameters. MCI and NC subjects were more affected by muscle weakness than WMH for global gait function ($r_s = 0.42$, $P < 0.001$ and $r_s = 0.23$, $P = 0.046$, respectively).

Conclusions   Persons with AD showed a predominant association between WMH and gait disturbance compared with MCI and NC subjects, and regional WMH had a detrimental effect on specific gait changes.

Keywords   Alzheimer's disease; Cerebral small vessel disease; Mild cognitive impairment; Muscle weakness; Gait; White matter hyperintensities

Introduction

Gait disturbances are common in older people and have important consequences for loss of functional independence and mortality.[1,2] Persons with Alzheimer's disease (AD) show decreased gait speed and impaired balance control correlating with the clinical course of dementia.[3,4] Alterations in body composition and muscle weakness are also shown even in the early stage of AD.[3] These musculoskeletal changes are considered a contributor to reduced physical performance.[5] In addition, complex gait control requires the integration of neural networks, including cortical, subcortical, and spinal cord structures.[6] Therefore, vascular dysfunction, which is very common in persons with AD, is also considered to be involved in their gait disturbance.

Cerebral small vessel disease (SVD) is frequently found in individuals with AD, and features seen on neuroimaging usually include white matter hyperintensities (WMH), lacunes, enlarged perivascular spaces (PVS), and cerebral microbleeds (CMB).[7] These features are not only associated with cognitive impairment but also have been widely considered an important vascular cause of gait disturbance.[8–11] Persons with AD show regional differences in WMH distribution compared with healthy individuals, and regional WMH are differentially associated with specific balance control.[10,12] In the clinical setting, gait function is generally assessed by gait speed due to its ease of measurement. However, gait speed is affected by multiple aspects of spatio-temporal gait function, such as pace, rhythm, postural control, and variability, which are considered to represent different features of specific neural control and functional substrates.[6] Moreover, these spatio-temporal gait parameters can be used to predict future gait speed.[13] Therefore, multifaceted gait assessment is necessary to detect early changes in gait.

To date, it is unclear whether WMH are more likely to affect gait function in persons with AD than in individuals with mild cognitive impairment (MCI) and normal cognition (NC). Furthermore, the impact of regional WMH on specific gait changes have not yet been clarified. To clarify these associations, it is necessary to adjust musculoskeletal confounders and evaluate gait function using quantitative gait assessment. The aims of this study were therefore (i) to clarify whether WMH are predominantly associated with gait disturbance in AD subjects compared with MCI and NC subjects and (ii) to clarify the regional impact of WMH on specific gait changes after adjusting for potential confounders. We hypothesized that WMH would have a greater impact on gait function in AD subjects and that regional WMH would have a detrimental effect on specific gait functions.

Methods

Participants

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology (NCGG) (approval no. 1429). All patients and their caregivers provided written informed consent before participating in the study.

We included 396 outpatients who visited the NCGG hospital between 2014 and 2018. The subjects were aged 65 years or older and had a diagnosis of AD (*n* = 187), MCI (*n* = 118), or NC (*n* = 91). The diagnosis of probable or possible AD was based on the findings of the National Institute on Aging/ Alzheimer's Association workgroups on the diagnostic guidelines for AD.[14] MCI was diagnosed based on the criteria defined by Petersen *et al.*[15] Persons with NC visited the NCGG hospital with suspected memory disorder, but they were diagnosed with NC. Subjects meeting the following criteria were excluded from this study: (i) subjects using walking assistance instruments such as canes and walkers; (ii) subjects with a history of stroke or cortical lesions; (iii) subjects with severe conditions such as cardiac failure, renal disorder, or liver dysfunction; and (iv) subjects with neurological disorders other than AD or MCI.

Clinical assessment

Clinical data were obtained from the NCGG Medical Genome Center Biobank, which collects clinical and biological material for biomedical research. Information regarding diagnoses, clinical information, and medication use was obtained from clinical charts. Subjects' global cognition was assessed by the Mini-Mental State Examination (MMSE),[16] and basic activities of daily living (ADL) was assessed by the Barthel index.[17] Polypharmacy was defined as taking five or more types of oral medicine.[18] We assessed the use of medication to treat AD, anxiety disorders, sleeping disorders, and psychotic disorders because these medications affect gait function.[19]

Musculoskeletal assessment

Body composition was assessed by bioelectrical impedance analysis (MC-180; Tanita Corp., Tokyo, Japan). Low muscle mass was defined as low skeletal muscle mass index (SMI), which was calculated as appendicular muscle mass divided by height squared (kg/m^2). Low SMI was defined as SMI <7.0 kg/m^2 for men and <5.7 kg/m^2 for women.[20] Low

muscle strength was defined as low hand grip strength, which was measured with a digital force gauge (ZP 500N; Imada, Toyohashi, Japan). Low grip strength was characterized as <28 kg for men and <18 kg for women.[20]

Quantitative gait assessment

Gait function was assessed using an electronic walkway (MW-1000, Anima Inc., Tokyo, Japan). Participants walked continuously for 6.4 m at their usual walking speed. Gait was evaluated as participants walked for 2.4 m on carpet; they started walking 2 m in front of the carpet and continued until they had walked 2 m beyond it so that their steady-state walking could be evaluated. Participants walked for two trials, and the mean values were used for analysis. We selected the following gait parameters because they sensitively reflect spatio-temporal gait changes and have shown association or unclear relevance to SVD.[6,8,9,11] Global gait function was indicated by (i) gait speed (cm/s); the pace domain was assessed by (ii) cadence (steps/min) and (iii) stride length (cm); the rhythm domain was determined by (iv) stride time (s) and (v) double-leg support time (s); the postural control domain was defined as the (vi) walking angle (degree) and (vii) step width (cm); and the variability domain was indicated by (viii) gait speed variability (%). Variability was calculated as the coefficient of variation: standard deviation/mean × 100. The gait parameters of the rhythm and postural control domains were measured on the left leg side. The stride length was divided by height to minimize the different foot lengths, and this value was used for all analyses.

Brain imaging

Images of the brain were acquired on a 1.5 Tesla magnetic resonance (MR) scanner (Philips Ingenia, the Netherlands) with T1-weighted (T1W), T2-weighted (T2W), T2*-weighted (T2*W), and fluid-attenuated inversion recovery (FLAIR) sequences. Markers of SVD were evaluated by visual analysis and computer methods.

In the visual analysis, WMH were identified as lesions that appeared as punctate or diffuse regions of hyperintense signals on T2W and FLAIR images. WMH were divided into periventricular hyperintensities (PVH) or deep white matter hyperintensities (DWMH), and these were assessed separately in four stages according to their severity.[21] Lacunes were defined as rounded or ovoid lesions (3 to 15 mm) in the white matter and sublobar regions, showing cerebrospinal fluid (CSF) signal intensity on T2W and FLAIR images and generally with surrounding hyperintense rims on FLAIR image. We counted the number and measured the volume of lacunes. Lacune volume was calculated by measuring the diameter of the lacune and assuming that the lesion was

spherical. PVS were defined as small (<3 mm) or linear hyperintensities in the unilateral basal ganglia on axial views of T2W image. CMB were defined as small (<5 mm), homogeneous, round foci of low signal intensity on T2*W images in the cortico-subcortical junction, white matter, and sublobar regions.

The distribution of WMH volume in each brain area was quantified using Software for Neuro-Image Processing in Experimental Research.[22] WMH were classified into PVH or DWMH, and the volumes of these lesions in the frontal, temporal, occipital, and parietal lobes and in the sublobar regions of the basal ganglia and thalamus were measured. When small cavitations were present in the middle of the WMH or mixed with hyperintensity lesions in the sublobar area, the volumes of these lesions were summed and included in the lesion volume for each brain area. Global brain atrophy was assessed by the parenchyma (PAR), which is the subtraction of CSF from intracranial (IC) volume, corresponding to the sum of total grey and white matter volumes. For analyses, the volume of lesions and the PAR were divided by the IC volume to minimize bias due to individual brain size. Further image acquisition parameters and methodological details are provided elsewhere.[22,23]

Statistical analysis

All analyses were performed using SPSS for Windows Version 26.0 (IBM Corp., Armonk, NY, USA). Normality of distributions was assessed with the Shapiro–Wilk test. Differences in clinical characteristics between AD, MCI, and NC subjects were examined by analysis of variance with Tukey's test as a post hoc analysis (for parametric variables) or the Kruskal–Wallis test (for non-parametric variables). Categorical variables were analysed by the χ^2 test. To examine the difference in gait performance in SVD severity, AD subjects were categorized as those with and without SVD. The presence of WMH was defined as ≥2 Fazekas grade PVH and/or DWMH. The presence of lacunes and that of CMB were defined as the presence of one or more lesions. The presence of PVS was defined as moderate to severe (11 or more).[24] All gait parameters were converted to z-scores referenced to NC subjects as zero, and analysis of variance was used to test the differences in AD subjects with and without SVD, MCI subjects, and NC subjects. To examine the associations of WMH volume and musculoskeletal factors on gait functions, we conducted partial Spearman rank order correlation analysis. Differences in gait function related to the number of lacunes, PVS, and CMB were evaluated by analysis of covariance. Finally, to identify the association between regional WMH volume and gait function, partial Spearman rank order correlation analysis was conducted by adjusting for classical confounders (age, MMSE, brain atrophy, and medications) and

musculoskeletal factors (SMI and muscle strength). Statistical significance was set at $P < 0.05$.

Results

Clinical characteristics

The characteristics of the participants are shown in *Table* 1. Persons with AD were older, had fewer years of education,

and had lower MMSE scores than MCI and NC subjects. The Barthel index score was slightly lower in AD subjects, but the basic ADL of all subjects was maintained. Regarding musculoskeletal function, AD subjects tended to have a lower SMI, but this was not statistically significant. However, the prevalence of low grip strength was significantly higher in AD subjects than in NC subjects. Regarding gait characteristics, AD subjects showed slow gait speed, shorter stride length, extended double-leg support time, increased walking angle, and greater gait speed variability. Regarding MR imaging characteristics, visual analysis showed that AD subjects

Table 1 Characteristics of the study population (*N* = 396)

	AD (n = 187)	MCI (*n* = 118)	NC (*n* = 91)
Demographic characteristics			
Age, years	77.5 (5.0)[*, †]	75.5 (5.0)[*]	73.2 (4.9)
Male, *n* (%)	60 (32.1%)	45 (38.1%)	38 (41.8%)
Education, years	10.5 (2.2)[*, †]	11.5 (2.6)[*]	12.6 (2.7)
Mini-Mental State Examination	19.3 (4.0)[*, †]	25.3 (3.1)[*]	28.2 (1.9)
Barthel index	97.9 (5.9)[*, †]	99.4 (2.0)	99.7 (1.9)
Hypertension, *n* (%)	97 (51.9%)	49 (41.5%)	35 (38.5%)
Diabetes mellitus, *n* (%)	27 (14.4%)	15 (12.7%)	8 (8.8%)
Medications			
Polypharmacy, *n* (%)	62 (33.2%)	40 (33.9%)	32 (35.2%)
Treat dementia, *n* (%)	52 (28.9%)[*, †]	9 (7.6%)	1 (1.1%)
Treat anxiety/sleeping/psychotic disorders, *n* (%)	42 (22.5%)	27 (22.9%)	23 (25.3%)
Musculoskeletal function			
Skeletal muscle mass index	6.5 (1.0)	6.7 (1.0)	6.7 (1.1)
Low grip strength, *n* (%)	94 (51.1%)[*]	42 (38.2%)[*]	15 (17.4%)
Gait characteristics			
Gait speed, cm/s	99.0 (20.8)[*, †]	105.4 (22.9)[*]	114.0 (19.1)
Cadence, steps/min	113.6 (12.2)	115.3 (12.0)	116.4 (9.5)
Stride length, cm	103.7 (16.0)[*]	108.7 (17.7)[*]	116.4 (15.7)
Stride time, s	1.07 (0.12)	1.06 (0.12)	1.04 (0.09)
Double-leg support time, s	0.13 (0.03)[*]	0.13 (0.03)	0.12 (0.02)
Walking angle, degree	9.0 (4.3)[*]	9.0 (4.1)	7.7 (3.1)
Step width, cm	7.9 (3.3)	8.3 (3.2)	7.7 (2.9)
Gait speed CV, %	5.2 (4.0)[*]	5.0 (3.6)	3.8 (2.8)
Neuroimaging characteristics			
Visual analysis			
Fazekas grade PVH	2.0 (0.7)[*]	1.9 (0.6)	1.8 (0.7)
Fazekas grade DWMH	1.5 (0.8)[*]	1.3 (0.8)	1.1 (0.7)
Number of lacunes	0.7 (1.4)	0.5 (1.1)	0.4 (1.4)
Volume of lacunes, mL	0.04 (0.12)[*]	0.03 (0.10)	0.01 (0.07)
Presence of lacunes, *n* (%)	52 (27.8%)	28 (23.7%)	15 (16.5%)
Presence of PVS, *n* (%)	62 (33.2%)	30 (25.4%)	25 (27.5%)
Presence of CMB, *n* (%)	44 (23.5%)	19 (16.1%)	14 (15.4%)
Computer analysis			
IC, mL	1432.1 (129.7)[*]	1447.2 (138.3)	1482.6 (122.8)
PAR, mL	1133.9 (105.3)[*, †]	1174.1 (120.8)	1219.6 (105.9)
WMH total, mL	16.6 (18.1)[*]	11.5 (11.2)[*]	7.4 (8.6)
Frontal lobe, mL	9.7 (10.2)[*]	6.7 (6.3)[*]	4.4 (4.6)
Temporal lobe, mL	1.0 (1.3)[*]	0.7 (0.8)[*]	0.5 (1.0)
Occipital lobe, mL	0.8 (0.9)[*]	0.7 (0.8)[*]	0.4 (0.5)
Parietal lobe, mL	5.1 (6.6)[*]	3.5 (4.3)[*]	2.2 (3.2)
PVH, mL	15.8 (18.1)[*]	11.0 (11.0)[*]	7.0 (8.4)
DWMH, mL	0.8 (1.3)	0.6 (0.9)	0.5 (0.9)
Sublobar lesions			
Basal ganglia, mL	0.23 (0.54)[*]	0.15 (0.39)	0.09 (0.36)
Thalamus, mL	0.04 (0.13)[*]	0.02 (0.06)	0.01 (0.10)

AD, Alzheimer's disease; CMB, cerebral microbleeds; CV, coefficient of variation; DWMH, deep white matter hyperintensities; IC, intracranial; MCI, mild cognitive impairment; NC, normal cognition; PAR, parenchyma; PVH, periventricular hyperintensities; PVS, perivascular spaces; WMH, white matter hyperintensities.
Data are presented as the mean (standard deviation) or numbers (%).
[*] $P < 0.05$, versus NC.
[†] $P < 0.05$, versus MCI.

had greater PVH and DWMH. The presence of lacunes, PVS, and CMB tended to be higher in AD subjects, but the difference was not statistically significant. Computer analysis showed that AD subjects had more WMH in all brain lobes, and these lesions were mostly prevalent in the periventricular area. Additionally, sublobar lesions in the basal ganglia and thalamus were greater in AD subjects than in NC subjects.

Gait changes in clinical groups

Differences in gait performance in each clinical group are shown in *Figure* 1. AD subjects with WMH showed slow gait speed ($P < 0.001$), shorter stride length ($P < 0.001$), prolonged stride time ($P = 0.042$), extended double-leg support time ($P = 0.012$), greater walking angle ($P = 0.022$), and

increased gait speed variability ($P = 0.005$) compared with NC subjects. AD subjects with WMH tended to reduce their cadence, but this difference was not statistically significant ($P = 0.119$). AD subjects with WMH showed slower gait speed than those without WMH ($P = 0.042$). However, other gait parameters were not statistically significant (stride length $P = 0.055$, stride time $P = 0.186$, double-leg support time $P = 0.060$, walking angle $P = 0.166$, gait speed variability $P = 0.178$). This may be due to the small sample size of AD subjects without WMH. Remarkably, AD subjects without WMH maintained the same level of gait function as MCI subjects.

AD subjects with lacunes, PVS, and CMB showed slow gait speed (all $P < 0.001$). The spatio-temporal gait parameters of AD subjects with lacunes and PVS were similar to those of AD subjects with WMH, showing reduced stride length and increased gait speed variability. AD subjects with CMB showed
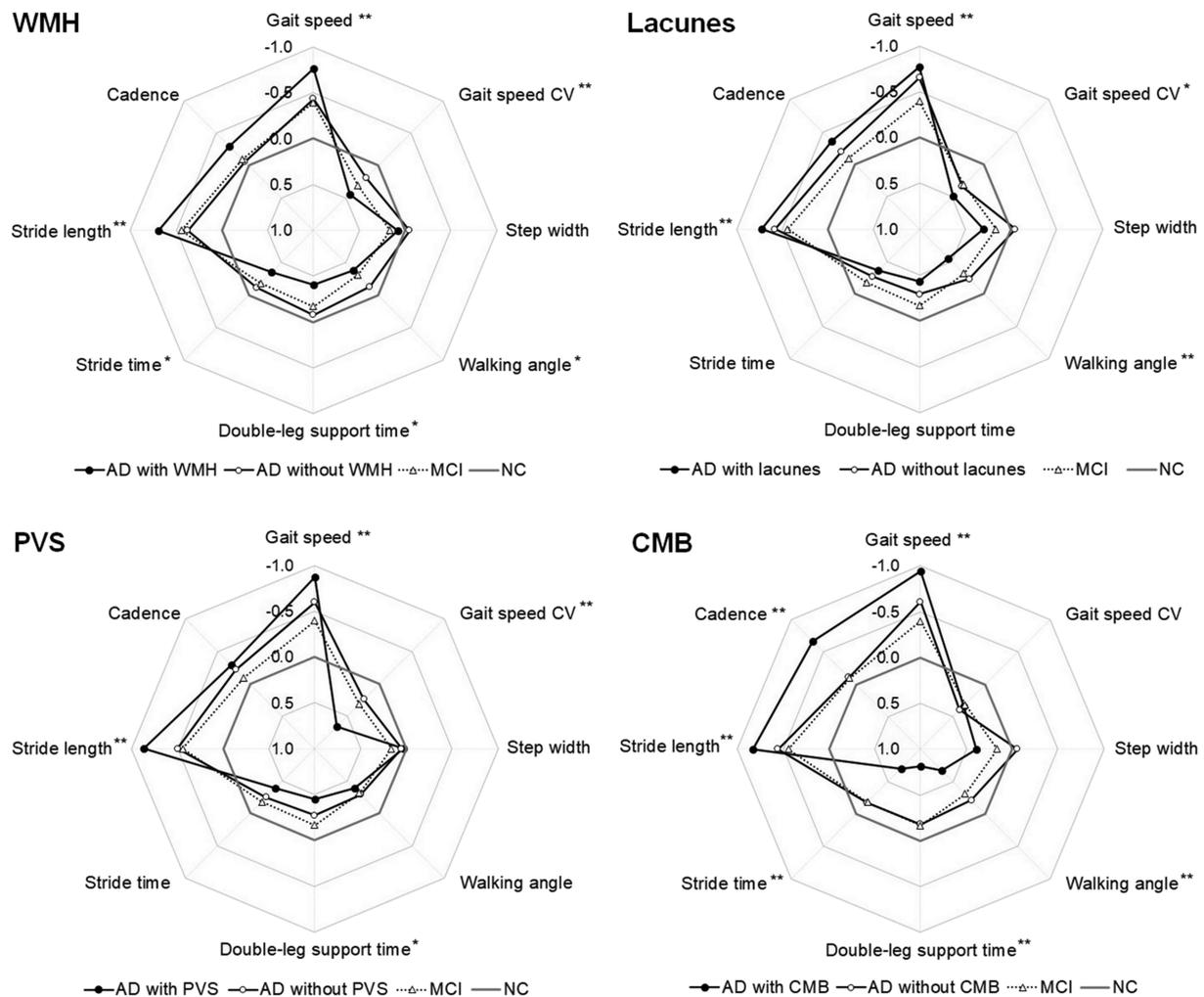

Figure 1 Differences in gait performance in each clinical group. Analysis of variance. The number of AD subjects with WMH was 142, and the number of AD subjects without WMH was 45. Indicates z-value differences in AD with SVD, AD without SVD, and MCI referenced to NC subjects as zero. **$P < 0.01$, *$P < 0.05$, AD with SVD against NC subjects. AD, Alzheimer's disease; CMB, cerebral microbleeds; CV, coefficient of variation; MCI, mild cognitive impairment; NC, normal cognition; PVS, perivascular spaces; SVD, small vessel disease; WMH, white matter hyperintensities.

decreased cadence; this spatio-temporal gait change differed from the changes observed in AD subjects with other SVD markers.

Association of white matter hyperintensities and musculoskeletal factors with gait functions

Next, we examined associations between WMH and musculoskeletal factors on gait functions in AD, MCI, and NC subjects (*Table* 2). We selected six parameters that significantly decreased in AD subjects with WMH in a previous analysis (*Figure* 1). Because the prevalence of vascular risk factors in AD subjects with and without WMH did not differ in this study (hypertension was present in 55.6% of AD subjects with WMH and in 40.0% of AD subjects without WMH, *P* = 0.067; diabetes was present in 14.8% of AD subjects with WMH and in 13.3% of AD subjects without WMH, *P* = 0.809, χ^2 test), classical factors such as age, MMSE, brain atrophy, and medication use, in addition to musculoskeletal factors, were adjusted for when the relationship between WMH and gait parameters was examined.

In AD subjects, PVH were associated with slower gait speed, prolonged stride time, extended double-leg support time, and increased walking angle. Additionally, sublobar lesions were associated with slower gait speed, prolonged stride time, and greater gait variability. Notably, reduced stride length was shown in AD subjects with WMH (*Figure* 1); however, this association was no longer evident after adjusting for classical and musculoskeletal factors. In MCI subjects, neither PVH nor DWMH was associated with any gait parameters, and only sublobar lesions were associated with shorter stride length and greater walking angle. In NC subjects, none of the WMH markers had adverse effects on any gait function.

Regarding musculoskeletal factors, AD subjects were found to have only muscle weakness and shorter stride length. Conversely, muscle weakness seemed to have a greater impact on gait function in MCI and NC subjects. Muscle weakness was associated with slower gait speed, shorter stride length, and prolonged double-leg support time in MCI and NC subjects and was further associated with walking angle in NC subjects.

Effects of lacunes, perivascular spaces, and cerebral microbleeds on gait functions

AD subjects with more lacunes, PVS, and CMB showed slower gait speed (*P* < 0.001). However, this difference was no longer significant after adjustment for classical and musculoskeletal factors (*Figure* 2). These SVD markers were associated with only slight changes in gait; AD subjects with more lacunes showed increased walking angle (*P* = 0.018), AD subjects with more PVS showed greater gait variability (*P* = 0.020), and AD subjects with more CMB showed reduced cadence (*P* = 0.037), prolonged stride time (*P* = 0.043), and extended double-leg support time (*P* = 0.008). Additionally,

Table 2 Association of white matter hyperintensities and musculoskeletal factors with gait function in Alzheimer's disease, mild cognitive impairment, and normal cognition subjects

		Gait speed		Stride length		Stride time		Double-leg support time		Walking angle		Gait speed CV	
		r_s	P	r_s	P	r_s	P	r_s	P	r_s	P	r_s	P
WMH markers													
AD	PVH	−0.18	**0.018**	−0.13	0.087	0.21	**0.006**	0.20	**0.009**	0.19	**0.013**	0.11	0.173
	DWMH	0.04	0.563	−0.01	0.859	−0.02	0.804	0.03	0.688	−0.15	0.059	−0.06	0.415
	Sublobar	−0.17	**0.025**	−0.10	0.190	0.20	**0.008**	0.13	0.090	0.11	0.166	0.19	**0.014**
MCI	PVH	−0.14	0.186	−0.12	0.228	0.09	0.395	0.13	0.213	0.14	0.159	0.12	0.241
	DWMH	0.07	0.515	0.09	0.363	−0.03	0.805	0.02	0.874	−0.04	0.698	−0.04	0.669
	Sublobar	−0.20	0.053	−0.24	**0.016**	0.15	0.139	0.13	0.204	0.32	**0.002**	−0.05	0.642
NC	PVH	−0.05	0.654	−0.09	0.446	0.01	0.965	0.04	0.726	0.08	0.474	−0.03	0.781
	DWMH	−0.04	0.729	−0.08	0.491	−0.13	0.264	−0.02	0.856	0.09	0.436	−0.22	**0.049**
	Sublobar	0.00	0.984	−0.13	0.245	0.00	0.980	0.08	0.493	−0.05	0.655	−0.02	0.842
Musculoskeletal factors													
AD	SMI	−0.01	0.945	−0.04	0.631	−0.09	0.256	0.13	0.100	0.09	0.216	−0.06	0.427
	Muscle strength	0.13	0.081	0.16	**0.033**	0.02	0.784	−0.10	0.203	−0.05	0.476	−0.02	0.752
MCI	SMI	0.02	0.870	−0.06	0.516	−0.09	0.354	0.17	0.096	0.14	0.172	0.04	0.718
	Muscle strength	0.42	**<0.001**	0.39	**<0.001**	−0.15	0.123	−0.22	**0.025**	−0.18	0.068	−0.17	0.082
NC	SMI	−0.08	0.486	0.07	0.555	0.15	0.178	0.18	0.113	0.01	0.951	0.01	0.901
	Muscle strength	0.23	**0.046**	0.27	**0.015**	−0.02	0.882	−0.22	**0.049**	−0.28	**0.013**	0.01	0.927

AD, Alzheimer's disease; CV, coefficient of variation; DWMH, deep white matter hyperintensities; MCI, mild cognitive impairment; NC, normal cognition; PVH, periventricular hyperintensities; SMI, skeletal muscle mass index; WMH, white matter hyperintensities.
Partial Spearman rank order correlation. All analyses were adjusted for age, Mini-Mental State Examination scores, brain atrophy, and medication use (to treat AD and anti-anxiety/sleeping/psychotic disorders). The relationship between WMH markers and gait functions was further adjusted for musculoskeletal factors (presence of low SMI and low muscle strength). The relationship between musculoskeletal factors and gait functions was further adjusted for sex and total WMH volume. Sublobar lesions were summed lesions in the basal ganglia and thalamus. Significant *P* values are in bold.
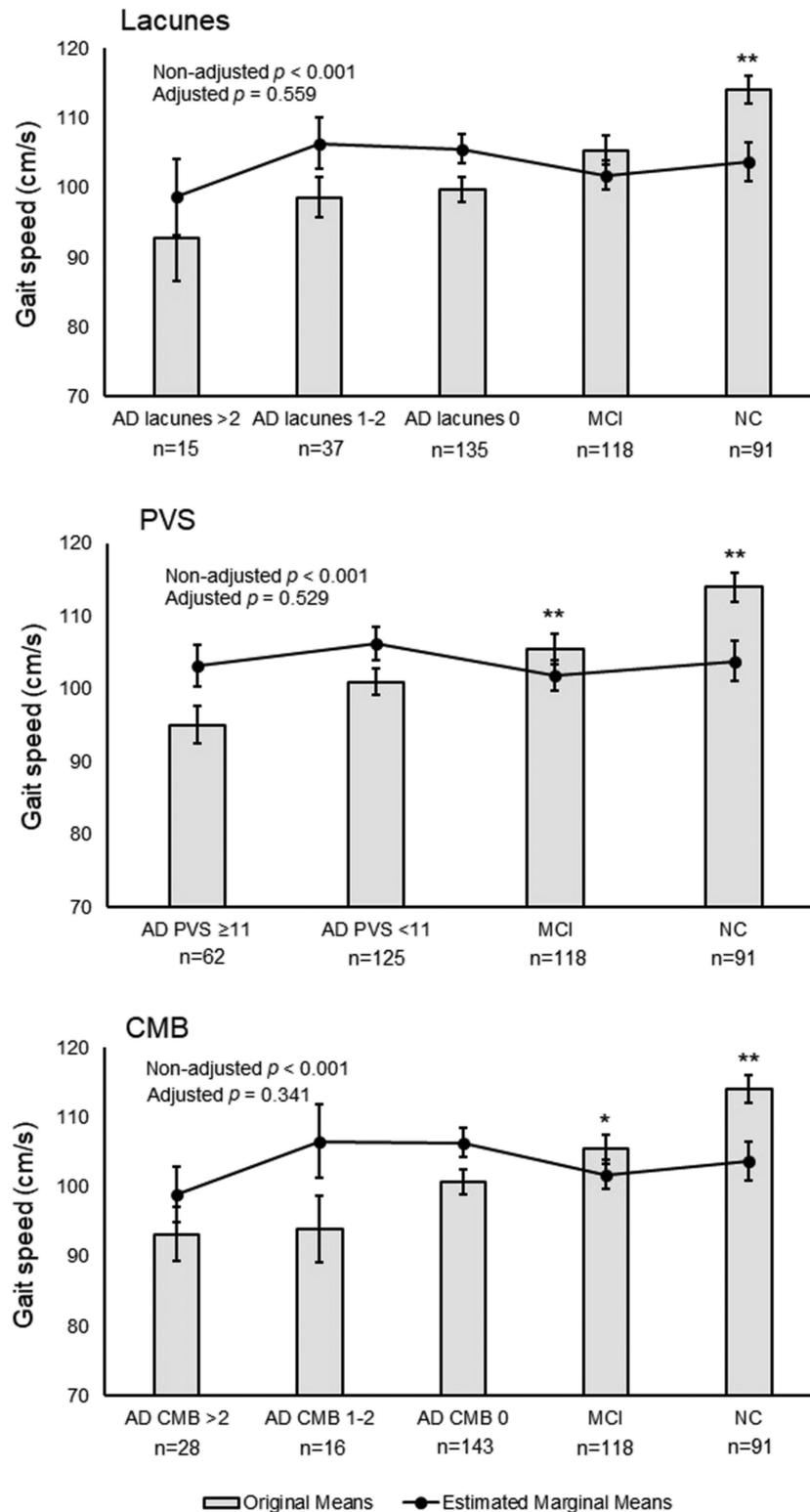
Figure 2 Differences in gait performance as a function of the number of lacunes, PVS, and CMB. The bars show the averages of the measured values. The line graphs show the estimated marginal means accounting for age, Mini-Mental State Examination score, brain atrophy, medication use (to treat AD and anti-anxiety/sleeping/psychotic disorders), and musculoskeletal factors (presence of low skeletal muscle mass index and low muscle strength). The error bars represent standard error. **$P < 0.01$, *$P < 0.05$, against AD subjects with lacunes > 2, PVS ≥ 11, and CMB > 2. AD, Alzheimer's disease; CMB, cerebral microbleeds; MCI, mild cognitive impairment; NC, normal cognition; PVS, perivascular spaces.

lacune volume assessed by visual analysis was not associated with gait speed ($r_s = -0.02$, $P = 0.817$) and all parameters indicating slight changes in gait.

Regional white matter hyperintensities and gait function

Finally, we examined associations between regional WMH and gait function in AD subjects (*Table* 3). PVH were associated with several gait parameters, whereas DWMH were not in the previous analysis (*Table* 2). Therefore, we further separated PVH in each brain lobe and investigated the association between regional PVH and gait parameters.

The PVH in the frontal and parietal lobes showed similar associations with gait parameters; that is, these lesions were significantly associated with slower gait speed, prolonged stride time, extended double-leg support time, and increased walking angle. Additionally, PVH in the temporal lobe was associated with prolonged stride time and extended double-leg support time. Sublobar lesions in the basal ganglia and thalamus were significantly associated with slower gait speed, prolonged stride time, and increased gait speed variability.

Discussion

This study revealed that persons with AD showed a predominant association between WMH and gait disturbance compared with MCI and NC subjects. Regional WMH had an especially detrimental impact on specific gait performance in AD subjects. PVH in the frontal and parietal lobes were associated with slow gait speed and changes in stride time, double-leg support time, and walking angle. Additionally, sublobar lesions in the basal ganglia and thalamus were associated with slow gait speed, changes in stride time, and increased gait speed variability. MCI subjects were found only

to have an association between sublobar lesions and gait parameters, and NC subjects did not show any associations between WMH and gait parameters. MCI and NC subjects were more affected by muscle weakness than WMH for gait disturbance.

AD subjects showed a predominant association of WMH with gait disturbance compared with MCI and NC subjects. Vascular lesions are common findings in AD subjects, and a large neuropathological study revealed that 80% of subjects diagnosed with AD had vascular pathology.[25] Several factors are related in a complex way to vascular alterations in subjects with AD. Cerebral amyloid angiopathy (CAA) is found in almost all subjects with AD and might be the underlying cause of WMH because CAA induces cerebral hypoperfusion in the white matter as a result of amyloid β deposition in microvessels.[12] In addition to CAA, arteriosclerosis and lipohyalinosis are also increased in the AD brain.[26] The development of CAA begins in cortical vessels in each lobe of the brain, while arteriosclerosis and lipohyalinosis commence in the basal ganglia and the deep white matter, and both expand to the entire brain. These vascular lesions are associated with amyloid β deposition and neurofibrillary tangle generation.[26] Moreover, the apolipoprotein ε4 genotype causes vascular dysfunction by affecting Aβ clearance in the brain.[27] Thus, AD-related pathology is thought to be involved in the development of WMH. Generally, gait functions decrease according to cognitive decline.[28] In addition, muscle weakness progresses with the clinical course of dementia.[3] Nevertheless, we found independent associations between WMH and gait disturbance after controlling for cognitive impairment and musculoskeletal changes. Moreover, our study showed that AD subjects without WMH maintained the same level of gait function as MCI subjects. Therefore, our observations suggest that distribution of the WMH burden in specific brain regions might have additional adverse impacts on gait function in AD subjects.

Disruption of white matter integrity has been considered the pathogenesis of gait impairment in subjects with

Table 3 Associations between regional white matter hyperintensities and gait performance in Alzheimer's disease subjects

	Gait speed		Stride length		Stride time		Double-leg support time		Walking angle		Gait speed CV	
	r_s	P	r_s	P	r_s	P	r_s	P	r_s	P	r_s	P
White matter lesions												
PVH in the frontal lobe	−0.21	**0.007**	−0.15	0.057	0.21	**0.007**	0.20	**0.008**	0.21	**0.007**	0.14	0.069
PVH in the temporal lobe	−0.11	0.158	−0.08	0.277	0.19	**0.013**	0.15	**0.049**	0.11	0.147	0.03	0.692
PVH in the occipital lobe	0.00	0.953	0.03	0.683	0.14	0.076	0.04	0.623	0.10	0.214	−0.03	0.669
PVH in the parietal lobe	−0.18	**0.019**	−0.14	0.073	0.22	**0.004**	0.20	**0.008**	0.20	**0.009**	0.09	0.264
Sublobar lesions												
Basal ganglia	−0.16	**0.034**	−0.10	0.194	0.19	**0.012**	0.11	0.154	0.11	0.173	0.16	**0.034**
Thalamus	−0.18	**0.023**	−0.14	0.062	0.16	**0.041**	0.13	0.085	0.05	0.480	0.20	**0.010**

CV, coefficient of variation; PVH, periventricular hyperintensities.
Partial Spearman rank order correlation. Adjusted for age, Mini-Mental State Examination scores, brain atrophy, medication use (to treat Alzheimer's disease and anti-anxiety/sleeping/psychotic disorders), and musculoskeletal factors (presence of low skeletal muscle mass index and low muscle strength). Significant *P* values are in bold.

WMH.[9,29] Proper gait requires sensory integration, motor planning, and execution of gait; these aspects largely rely on cortical–subcortical neuronal networks.[28] Frontal and temporoparietal cortices correspond with one another to receive and integrate sensory information; these cortices also play a critical role in the execution of gait with subcortical motor structures.[28] In this study, PVH in the frontal, temporal, and parietal lobes were associated with several gait parameters, whereas DWMH were not. Periventricular white matter, especially in the frontal region that contains major subcortical motor circuits, has longitudinal fibres that subserve gait and balance control.[30] In addition, we found associations between lesions in the basal ganglia and thalamus and subtle gait changes, including greater gait variability. Gait variability indicates walking fluctuation due to loss of gait rhythmicity and diminished balance control. The basal ganglia and thalamus are functionally regarded to be involved in higher-order regulation of posture control. Damage to these regions disrupts volitional processes of gait control and impairs postural adjustment, which leads to increased gait variability.[31,32] Thus, higher gait function that requires integration of sensory, motor execution, and postural control relies on widespread neural networks, and disruption of networks by PVH and sublobar lesions may lead to instability in gait.

Some studies have reported that stride length is a sensitive marker for gait abnormalities in subjects with WMH.[8,29] However, we did not find any relationship between regional WMH and stride length in AD subjects. AD subjects with WMH exhibited shorter stride lengths, but this association was no longer observed after adjusting for classical confounders. Conversely, muscle weakness was significantly associated with shorter stride length after adjusting for WMH. Previous studies indicated that step length was associated with more cortical atrophy rather than atrophy in subcortical regions, especially evident in the reduced grey matter volume in the parietal and occipital lobes.[6] Our results imply that AD subjects with reduced stride length are more susceptible to brain atrophy and muscle weakness than WMH. In addition, the same pace domain as stride length, decreased cadence, was not shown in AD subjects with WMH. A similar lack of association of decreased cadence with WMH[8] and with loss of white matter integrity has been identified.[9] In this study, only CMB showed an association with decreased cadence. Consistent with previous studies, our observations suggest that these aspects of gait might be less influenced than others by damage to white matter regions. Our study found associations between regional WMH and other gait parameters, such as stride time, double-leg support time, walking angle, and gait variability. Importantly, WMH regions that were related to these gait parameters were also associated with decreased gait speed. This indicates that global gait disturbance

due to regional WMH could be caused by these spatio-temporal gait changes. On the other hand, although other SVD markers such as lacunes, PVS, and CMB appeared to be related to slight changes in gait, they were not associated with global gait function, suggesting that these SVD markers do not have a stronger impact on gait function than WMH.

Our previous study found that subcortical lesions in the occipital lobe were strong predictors of falls in AD and amnestic MCI subjects,[10] whereas the current study did not find any relationship between occipital lesions and gait parameters. The subcortical occipital region has longitudinal fibres that link fronto-orbital areas, motor areas, and visual conceptualization, and deficits in this tract could affect visuospatial processing in gait.[33–35] Our study evaluated gait function under conditions that did not require visuospatial processing. Therefore, gait parameters may be predominantly associated with PVH in the anterior region rather than posterior lesions. The long association fibres for motor control, especially in the inferior fronto-occipital fasciculus, pass through the periventricular white matter,[33] and this tract is more susceptible to WMH burden than other fibre tracts.[36] WMH are highly variable disease processes with growth and shrinkage, especially in AD subjects with a considerable amount of WMH.[37] A recent study indicated that controlling blood pressure was associated with a reduction in WMH and preserving white matter integrity in subjects with minor stroke.[38] Additionally, poor glucose management in diabetic patients with AD has been shown to be associated with frontal WMH.[39] Therefore, management of vascular risk factors potentially leads to better brain tissue outcomes and could lead to the maintenance of gait function.

Some methodological issues need to be considered. First, this study excluded subjects who used walking assistance devices, as the gait function of such individuals was thought to be more impaired than that of other individuals. Because regional WMH were closely associated with balance control,[10] the excluded subjects may have had more WMH than the included subjects. Therefore, our results may have underestimated the impact of WMH on gait function. Nevertheless, we found an association between WMH and gait changes, suggesting that WMH may be a sensitive marker for gait changes in persons with AD. Second, lacunes could not be completely distinguished from WMH by computer analysis. However, the volume of lacunes assessed by visual analysis was not associated with any gait parameters, and the number of lacunes also did not have a significant effect on gait function. Therefore, our results suggest that lesion volume burden in specific brain areas might have a great impact on gait function. Third, we used parenchymal volume as a marker of brain atrophy. However, WMH are associated with cortical thinning and cerebral atrophy, and regional

brain atrophy is associated with gait disturbance.[6,7] Therefore, estimating regional brain atrophy and using it as a confounder for the relation of regional WMH and gait function is more appropriate. Fourth, WMH-related gait disturbances are thought to be due to disrupted white matter tracts.[9,29] Therefore, evaluating microstructural white matter integrity, in addition to WMH, may further elucidate the role of motor networks of the brain in gait function. Finally, cognitive function was measured by the MMSE, which indicates global cognition. However, the cognitive domain in executive function is closely related to gait disturbance.[28] Therefore, assessing executive functions, such as attention, sensory integration, and motor planning, should be included in future studies.

In conclusion, AD subjects showed a predominant association between WMH and gait disturbance compared with MCI and NC subjects. Regional WMH were found to be associated with specific gait changes in AD subjects. Conversely, MCI and NC subjects showed a predominant association of muscle weakness and gait function than WMH. Our observations suggest the importance of multiple interventions to prevent WMH and muscle weakness, which could be useful for maintaining gait function in older populations.

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Conflicts of interest

The authors declare no conflicts of interest.

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