Table 2 Univariate analysis of factors related to volumes of white matter hyperintensity

	Frontal		Parietal		Temporal		Occipital	
	CC	*P*-value	CC	*P*-value	CC	*P*-value	CC	*P*-value
Age	0.59	<0.001	0.50	<0.001	0.45	<0.001	0.18	<0.001
sBP	0.31	<0.001	0.26	<0.001	0.22	<0.001	0.07	0.03
dBP	0.21	<0.001	0.17	<0.001	0.15	<0.001	0.03	0.27

CC, correlation coefficient; dBP, diastolic blood pressure; sBP, systolic blood pressure.

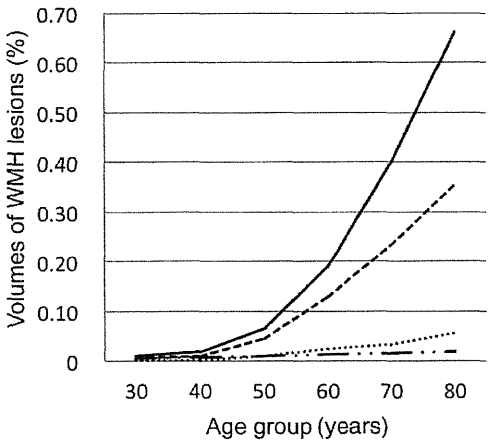

Figure 2 Mean volume of white matter hyperintensity (WMH) lesions by age groups according to cerebral lobes divided by the intracranial capacity. WMH lesions significantly enlarged by age. —, frontal; ----, parietal; ·····, temporal; and — ·, occipital.

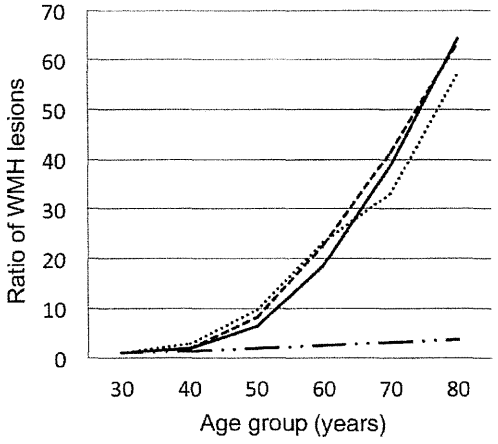

Figure 3 Mean volume of white matter hyperintensity (WMH) lesions by age groups according to the cerebral lobes in comparison to the value of the 30s age group as baseline. The rate of enlargement was slight only in the occipital lobe. —, Frontal; ----, parietal; ·····, temporal; and — ·, occipital.

internal carotid and the vertebral artery might be different, which could affect the results. Another example is posterior reversible encephalopathy syndrome, which is a disease causing reversible lesions mainly in the occipital or the parietal lobe by the elevation of systemic blood pressure. As the pathophysiology of this disorder, the occipital lobe is thought to be more vulnerable to the threshold of the autoregulation of the brain vasculatures than the other lobes, because the distribution of terminals of the sympathetic nervous system is low in the occipital lobe.[13,14] Therefore, breakthrough of the blood–brain barrier can lead to vasogenic edema, especially in the white matter of the occipital lobe. The autoregulatory capacity of the vertebrobasilar arteries is shifted lower than that of the internal carotid artery. Therefore, the threshold of breakthrough is lower, and the capacity of reserving the intracranial blood flow at the time of low systemic blood pressure is higher, which can lead to the hurdle of enlargement of the WMH lesions in the occipital lobe rather than the other lobes mainly fed by the internal carotid artery.

The present study using brain examinations during health check-up would reflect the distribution of WMH lesions in an almost healthy population, and thus, it would be helpful as a baseline of comparison in clinical settings. Evidence of difference of behavior in the occipital lobe by age that has different vascular background as discussed above could be the key for clarification of mechanisms of WMH lesions. We hope that further progress of anatomical investigation of brain vessels will lead to the prevention of the evolution of the aging phenomenon in the cerebral white matter. In addition, widespread application of quantitative assessment of WMH lesions with improved ease would further clarify the pathophysiology of WMH lesions of the brain in the future.

The present study had several limitations. The first might be a self-selection bias. Participants from a hospital-based health check-up were used, and therefore, they might have or pay attention to geriatric disease, or have a family history of stroke. Second, to prove the effect of aging, following the same patient population for longer than 20 years would be desirable. However, carrying out such a study would require a long period of data collection. The final limitation was

that we could not clarify the relationships of WMH lesions and their clinical significance including activities of daily living or quality of life. Further study would be required to clarify these points.

In conclusion, WMH lesions increased with age, and were associated with blood pressure based on computational quantitative volumetric analyses. However, the occipital lobe was the only exception to these findings.

Acknowledgments

This work was partially supported by Grants from Research Funding of Longevity Sciences (25-6) from the National Center for Geriatrics and Gerontology.

Disclosure statement

The authors declare no conflict of interest.

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Geriatr Gerontol Int 2015; **15 (Suppl. 1):** *81–85*

LETTERS TO THE EDITOR
RESEARCH STUDIES

Left ventricular diastolic dysfunction is directly associated with cerebral white matter lesions in elderly patients

Dear Editor,

Cerebral white matter lesions (WML) have been established to increase with age, and are associated with heightened risks of stroke,[1] cognitive decline[2] and depressive disorder.[3] We previously reported that the severity of left ventricular (LV) diastolic dysfunction is associated with the volume of cerebral WML.[4] However, the analysis could not be carried out by removing the effect of the common or specific risk factors that are known to be involved in the progression of LV diastolic dysfunction and/or cerebral WML, such as age, hypertension, diabetes mellitus, hyperlipidemia, smoking, obesity and so on. Consequently, whether LV diastolic dysfunction is directly associated with cerebral WML remained unclear. Therefore, to clarify this, we carried out a cross-sectional study by conducting further in-depth examination of these risk factors and also by increasing the study population.

The study registration period was from April 2010 to October 2013. Participants comprised 133 outpatients between aged 65 and 75 years with normal LV contraction (ejection fraction >50%) and no signs or history of symptomatic heart failure, ischemic heart diseases, atrial fibrillation, stroke, or cognitive dysfunction. We also excluded those patients with ≥50% stenosis in the carotid arteries on ultrasonography with 2-D and Doppler analysis. The volume of cerebral WML was quantified on brain magnetic resonance imaging using a fully automatic segmentation program[5] developed in the Department of Radiology at Leiden University Medical Center (Leiden, the Netherlands), and early diastolic mitral inflow and early diastolic mitral annular tissue velocity (E/E') ratio, a parameter that indicates the severity of LV diastolic dysfunction, was measured by tissue Doppler echocardiography.[6] A total of 20 4-h systolic and diastolic blood pressure were obtained by ambulatory blood pressure monitoring. In addition, LV ejection fraction, body mass index, estimated glomerular filtration rate, carotid intimal media thickness, and levels of plasma B-type natriuretic peptide, hemoglobin A1c and low density lipoprotein cholesterol were also determined. Values are shown as mean ± standard deviation unless otherwise stated. Data were analyzed using SPSS version 17.0 software (SPSS, Chicago, IL, USA). The study protocol was approved by the ethics/conflict of interest committee at the National Center for Geriatrics and Gerontology. Written informed consent was obtained from all participants before participation.

Table A shows the patient characteristics. The results of linear regression analysis between cerebral WML volume and estimated factors are shown in Table B. These results showed that four factors (age, systolic blood pressure, plasma B-type natriuretic peptide and E/E') had a significant correlation ($P < 0.05$) with cerebral WML volume. Based on the results, multivariate analysis was carried out in order to clarify the principal factors involved in the increase of the cerebral WML. As a result, E/E' and age had been shown to be significantly correlated with cerebral WML volume ($P < 0.01$), with the correlation greater for E/E' ($P = 0.003$) than for age ($P = 0.03$; Table C).

The present study clarified the direct association between the severity of LV diastolic dysfunction and the volume of WML in elderly patients even after removing the effects of risk factors that were involved in the progression of LV diastolic dysfunction and/or cerebral WML. The results can be interpreted in two ways. The first interpretation is that a common, but unknown, factor exacerbates both cerebral WML and LV diastolic dysfunction, with this complicating factor being profoundly involved in the onset and progression of both diseases. The second interpretation involves chronic low cardiac output and chronic cerebral ischemia. Some reports in recent years have suggested that cerebral perfusion is impaired in patients with chronic low cardiac output.[7–9] Thus, considering that cardiac output decreases with the decrease in blood flow into the LV from the left atrium as a result of the progression in LV diastolic dysfunction, and also considering that a chronic decrease in cerebral blood flow is thought to be the primary mechanism underlying cerebral WML formation, the present results can also be interpreted as suggesting that decreased cardiac output elicits chronic cerebral ischemia.[10] Further investigation is necessary to clarify these points.

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doi: 10.1111/ggi.12663

Table A Patients characteristics

	Total	Mean ± SD
n	133	
Men (*n*)	64	
Smoking episode (*n*)	42	
Age (years)		69.7 ± 3.2
BMI (kg/m^2)		23.6 ± 3.5
Echocardiographic data		
EF (%)		65.9 ± 4.8
E/E'		12.0 ± 3.7
SBP (mmHg)		129.0 ± 11.5
DBP (mmHg)		75.6 ± 7.2
IMT (mm)		0.7 ± 0.1
HbA1c (%)		5.9 ± 0.6
LDL-C (mg/dL)		109.6 ± 23.5
eGFR (mL/min/1.73 m^2)		69.0 ± 12.5
BNP (pg/mL)		27.0 ± 28.0
WML (mL)		6.5 ± 7.2
PVL (mL)		5.7 ± 6.3
DWML (mL)		0.8 ± 1.4

Table B Results of linear regression analysis

	β-coefficient	*r*-value	*p*-value
Sex	0.350	0.240	0.781
Smoking episode	2.368	0.144	0.098
Age	0.579	0.258	0.003*
BMI (kg/m^2)	0.038	0.017	0.834
Echocardiographic data			
EF (%)	0.023	0.014	0.890
E/E'	0.793	0.381	<0.001*
SBP (mmHg)	0.171	0.272	0.001*
DBP (mmHg)	0.083	0.082	0.345
IMT (mm)	8.995	0.141	0.104
HbA1c (%)	1.628	0.131	0.133
LDL-C (mg/dL)	0.020	0.063	0.469
eGFR (mL/min/1.73 m^2)	-0.007	0.010	0.897
BNP (pg/mL)	0.065	0.253	0.003*

Table C Results of multivariate analysis

	p-value
Age	0.030*
E/E'	0.003*
SBP (mmHg)	0.089
BNP (pg/mL)	0.611

*$p < 0.05$. BMI, body mass index; EF, ejection fraction; E/E', ratio of early diastolic mitral inflow (E) to early diastolic mitral annular tissue velocity (E'); SBP, systolic blood pressure; DBP, diastolic blood pressure; IMT, carotid intimal media thickness; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; BNP, plasma B-type natriuretic peptide; WML, white matter lesions; PVL, periventricular white matter lesions; DWML, deep subcortical white matter lesions.

Disclosure statement

The authors declare no conflict of interest.

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Geriatr Gerontol Int 2015; **15 (Suppl. 1):** *59–65*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Impact of night-time blood pressure on cerebral white matter hyperintensity in elderly hypertensive patients

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Aim: Cerebral white matter hyperintensity (WMH) is highly prevalent in the elderly population, and increases the risk of dementia and stroke. We investigated the relationship between ambulatory blood pressure monitoring levels and quantitatively measured WMH volumes among elderly hypertensive patients with well-controlled blood pressure (BP) to re-evaluated effective hypertension management methods to prevent the progression of WMH.

Methods: Participants comprised 84 hypertensive patients aged between 65 and 75 years without symptomatic heart failure, ischemic heart disease, atrial fibrillation, stroke or cognitive dysfunction.

Results: Linear regression analysis showed that office BP was not associated with WMH volume increases. Raised night-time systolic BP ($P = 0.013$) were associated with greater WMH volumes during ambulatory blood pressure monitoring. To clarify the effect of asleep systolic BP on WML volume, we then classified patients into two systolic BP groups as follows: <125 mmHg ($n = 47$) and ≥125 mmHg ($n = 37$). Baseline characteristics were almost similar in both groups, except the dipper type of circadian BP variation was significantly common in the group with night-time systolic BP <125 mmHg. However, WMH volume was greater in the group with night-time systolic BP ≥125 mmHg than that in the <125 mmHg group (9.0 ± 8.4 mL *vs* 4.1 ± 4.3 mL, $P = 0.015$).

Conclusion: Higher night-time systolic BP levels were observed to contribute greater WMH volumes in elderly hypertensive patients. To prevent the progression of WMH, controlling BP on the basis of ambulatory blood pressure monitoring is important. **Geriatr Gerontol Int 2015; 15 (Suppl. 1): 59–65.**

Keywords: ambulatory blood pressure monitoring, cerebral white matter hyperintensity, circadian blood pressure variation, night-time blood pressure, office blood pressure.

Introduction

Cerebral white matter hyperintensity (WMH) on brain magnetic resonance imaging (MRI) is highly prevalent in the elderly population, and increases the risk of stroke,[1,2] and cognitive[3,4] and mobility impairment.[5–7] Although believed to be vascular in origin, the exact etiology of WMH remains unknown.

Populations with hypertension, diabetes, metabolic syndrome, chronic kidney disease, high serum total homocysteine levels, a history of smoking and vitamin D deficiency have been reported as high-risk groups for WMH developing and becoming severe.[8–12] Furthermore, our group has clarified that left ventricular diastolic dysfunction is associated with WMH in elderly patients without ischemic heart disease and stroke.[13] Of the aforementioned risk factors, hypertension is considered the greatest risk factor for the progression of WMH. It has been reported that in patients with hypertension, the WMH grade is significantly worse in non-treated groups compared with that in the treated groups.[14] Other reports have shown that the WMH grade has a positive correlation with systolic and diastolic blood pressure (BP) of the arm,[15] as well as central arterial systolic BP,[16] and that WMH strongly correlates with a high 24-h mean BP, particularly high nocturnal BP and non-dipper type hypertension.[17,18] Therefore, it is considered that early aggressive BP management is important to prevent the progression of WMH. Studies carried out to date have primarily targeted patients aged in their 50s to 60s, and there is still limited information

Accepted for publication 17 September 2015.

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on the older population. Furthermore, the severity of WMH has been determined using grade classification on the basis of visual observation.

A method of quantifying WMH volume by processing images obtained by MRI, which enables quantitative evaluation, has recently been established. Geriatric syndromes, such as cognitive impairment, can develop at approximately 75–80 years-of-age, and from a prophylactic perspective, studies should be carried out that focus on elderly individuals before this stage. Therefore, we quantitatively measured WMH volume in elderly patients with hypertension, examined the relationship between clinical data, such as blood pressure, and re-evaluated effective management methods for hypertension to prevent the progression of WMH.

Methods

Participants

Hypertensive outpatients aged 65–75 years treated with regular antihypertensive agents by the Department of Cardiology at the National Center for Geriatrics and Gerontology, Obu, Japan, were recruited. Among these, patients with symptomatic heart failure, ischemic heart disease, valvular heart disease, atrial fibrillation, stroke, neurodegenerative disorder or clinically diagnosed dementia were excluded.

Age, sex, height, bodyweight and office BP were recorded. Thereafter, biochemical blood tests and other tests including 24-h ambulatory blood pressure monitoring (ABPM), carotid duplex ultrasound for measurement of intima media thickness, brachial-ankle pulse wave velocity and ankle brachial index were examined, and the relationships with WMH volume were analyzed.

The study protocol was approved by the ethics/conflict of interest committee at the National Center for Geriatrics and Gerontology. Written informed consent was obtained from all participants before participation.

Neuroimaging studies

WMH volume was measured according to the following procedure using MRI.

A standard series of axial T1-weighted (repetition time [TR], 485 ms; echo time [TE], 11 ms; matrix, 256 × 256), T2-weighted (TR, 3800 ms; TE, 93 ms; matrix, 352 × 352) and fluid-attenuated inversion recovery (FLAIR; TR, 8000 ms; TE, 101 ms; inversion time, 2500 ms; matrix, 256 × 256) MRI sequences were carried out using a 1.5-T MR system (Siemens Avanto, Muenchen, Germany). Scans were carried out parallel with the anterior commissure-posterior commissure line, with 6-mm thick slices and an interslice gap of 1.2 mm. MRI data were processed to measure total volumes of the intracranial space, parenchyma, ventricles and WMH using a fully automatic segmentation program (Software for Neuro-Image Processing in Experimental Research) developed in the Department of Radiology at Leiden University Medical Center (Leiden, the Netherlands). WMH were defined as hyperintense lesions on both FLAIR images and T2-weighted images. WMH connected to the lateral ventricles were labeled as periventricular hyperintensity (PVH). WMH not connected to the lateral ventricles were labeled as deep WMH. Detailed procedures for MRI post-processing using Software for Neuro-Image Processing in Experimental Research have been described elsewhere.[19]

ABPM

A validated ambulatory recorder (TM-2431; A&D, Tokyo, Japan) and cuff on the non-dominant arm were used to carry out ABPM. BP was measured at 30-min intervals for day (06.00–21.59 hours) and 1-h intervals for night (22.00–05.59 night). Night-time was defined as the period in bed given in the sleep diary entries. BP measured <10 times during daytime or <5 times during night-time, as the result of errors, were excluded from analysis. BP and heart rate, including 24-h mean value, mean daytime value and mean night-time value, were calculated from recorded measurements and used in data analyses. Non-dipper was defined as <10% fall in night-time systolic BP relative to daytime systolic BP.

Statistical analysis

Values are shown as mean ± standard deviation unless otherwise stated. The correlation between WMH and each clinical item was found by linear regression analysis. Differences among the two groups were analyzed using the χ^2-test or Fisher's exact test, Student's t-test and Welch's test. Values of $P < 0.05$ were considered significant. Data were analyzed using SPSS version 17.0 software (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 84 patients with hypertension were enrolled in the present cross-sectional study (mean age 69.7 ± 3.6 years), including 40 male patients (47.6%; Table 1). The mean body mass index was 23.4 ± 3.4, with no severe obesity or leanness observed. Antihypertensive therapy including calcium antagonists, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, diuretics, and beta-blockers were given to 46 patients (54.8%), 48 patients (57.1%), four patients (4.8%), 10 patients (11.9%) and 21 patients (25.0%), respectively. The number of antihypertensive agents administered included monotherapy in 33 patients (39.2%) and dual

Table 1 Patients' characteristics

Parameters	$n = 84$
Age (years)	69.7 ± 3.6
Male (%)	40 (47.6%)
Height (cm)	157.8 ± 8.3
Bodyweight (kg)	58.8 ± 10.4
BMI (kg/m^2)	23.4 ± 3.4
Diabetes	14 (16.7%)
Dyslipidemia	31 (36.9%)
Antihypertensive therapy	
Ca-antagonist	51 (60.7%)
ARB	54 (64.3%)
ACE-I	4 (4.8%)
Diuretics	13(15.5%)
βblocker	22 (26.1%)
No. of medications (%)	
1	36 (42.9%)
2	37 (44.0%)
3	10 (11.9%)
4	1 (1.2%)
IMT (mm)	0.67 ± 0.19
ABI	1.16 ± 0.17
baPWV (cm/s)	1788 ± 269
Biochemical test	
UA (mg/dL)	5.61 ± 1.46
BUN (mg/dL)	16.6 ± 4.6
Cr (mg/dL)	0.79 ± 0.20
LDL (mg/dL)	112.5 ± 24.4
HDL (mg/dL)	55.5 ± 12.8
TG (mg/dL)	133 ± 115
Glucose (mg/dL)	117 ± 30
HbA1c (%)	5.6 ± 0.6

ABI, ankle brachial index; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; Cr, creatinine; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL, low-density lipoprotein cholesterol; TG, triglyceride; UA, uric acid; UN, urea nitrogen.

therapy in 34 patients (40.4%), whereas triple therapy was administered to eight patients (9.5%), and quadruple agent therapy to one patient (1.2%). Furthermore, 14 patients (17.3%) had concurrent diabetes and 31 patients (36.9%) had concurrent dyslipidemia. Hemoglobin A1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and trigycleride values were 5.9 ± 0.6, 112.5 ± 24.4, 55.5 ± 12.8 and 133 ± 115, respectively.

Quantitative evaluation of WMH

Table 2 summarizes the result of quantitative evaluation on MRI. The WMH volume was 6.67 ± 8.03 mL, more than 80% of which was PVH, whereas there was very little deep WMH. The ratio of white matter lesion occupying the cerebrum (WMH/parenchyma) was 0.610 ± 0.740%. In addition, possible relationships between age, body mass index, blood and physiological tests with WMH were examined by linear regression analysis, but no correlations were found.

Table 2 Quantitative evaluation of magnetic resonance imaging

MRI imaging	
WMH (mL)	6.67 ± 8.03
PVH (mL)	5.83 ± 7.17
DWMH (mL)	0.83 ± 1.44
IC (mL)	1433 ± 128
PAR (mL)	1095 ± 104
PAR/IC (%)	76.4 ± 2.53
WMH/PAR (%)	0.610 ± 0.740

DWMH, deep subcortical white matter hyperintensity; IC, intracranial space; MRI, magnetic resonance imaging; PAR, parenchyma; PVH, periventricular white matter hyperintensity; WMH, white matter hyperintensity.

Office BP and ABPM

The results of BP measurement are shown in Table 3. Office BP was 133 ± 12/77 ± 8 mmHg, with heart rate of 72 ± 11 b.p.m., and most patients had good BP control. On BP analysis using ABPM, the 24-h mean BP, mean daytime BP, and mean night-time BP were 130 ± 11/75 ± 7 mmHg, 132 ± 11/78 ± 7 mmHg and 121 ± 14/69 ± 9 mmHg, respectively. Linear regression analysis showed no correlation between office BP and WMH; however, night-time mean systolic BP alone correlated to WMH with a significant difference ($r = 0.328$, $P = 0.013$).

On calculating the night–day systolic BP ratio as an indicator of circadian BP variation, a little less than half appeared to be in the dipper group (night–day systolic blood pressure ratio is 0.9 or less). Examination of the relationship with WMH volume showed that although this tendency to be in the dipper group was recognized, there was no statistical significance ($r = 0.251$, $P = 0.06$).

Two-group comparison based on night-time systolic BP

To clarify the effect of night-time mean systolic BP on WMH volume, we next classified patients into two night-time systolic BP groups as follows: <125 mmHg ($n = 47$) and ≥125 mmHg ($n = 37$).

A comparison of background factors based on mean night-time systolic BP is shown in Table 4. There was

Table 3 Relationship between blood pressure profiles and white matter hyperintensity volumes

	Mean ± SD	*r*	*P*
Office BP			
Systolic (mmHg)	133 ± 12	−0.052	0.69
Diastolic (mmHg)	77 ± 8	−0.022	0.86
HR (b.p.m.)	72 ± 11	0.121	0.36
ABPM			
All-day			
Systolic (mmHg)	130 ± 11	0.241	0.071
Diastolic (mmHg)	75 ± 7	0.074	0.58
HR (b.p.m.)	66 ± 8	−0.096	0.49
Day-time			
Systolic (mmHg)	132 ± 11	0.181	0.17
Diastolic (mmHg)	78 ± 7	0.039	0.77
HR (b.p.m.)	68 ± 9	−0.082	0.54
Night-time			
Systolic (mmHg)	121 ± 14	0.328	0.013
Diastolic (mmHg)	69 ± 9	0.171	0.2
HR (b.p.m.)	72 ± 11	0.015	0.91
Night-time/daytime systolic BP ratio	0.91 ± 0.8	0.251	0.06

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; HR, heart rate.

no significant difference observed for age, sex and BMI. Similar results were found for patients with concurrent diabetes, and there was no difference in hemoglobin A1c observed. Concurrent dyslipidemia tended to be common among patients in the group with higher night-time systolic BP; however, there was no statistical difference, and no significant difference was observed in intima media thickness, ankle brachial index, brachial-ankle pulse wave velocity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride. With regard to office BP and heart rate, there was no significant difference observed. Furthermore, the dipper type of circadian BP variation was significantly common in the group with lower night-time systolic BP. A comparison of WMH volume showed a significantly higher volume in the group with high mean night-time systolic BP (9.0 ± 8.4 mL *vs* 4.1 ± 4.3 mL, $P = 0.015$), which we found was primarily attributed to elevated PVH volumes (Fig. 1).

Furthermore, to assess the effect of circadian BP variation, WMH volumes of the dipper and non-dipper group were evaluated. In the group with lower night-time systolic BP, WMH volumes were similar in the dipper and non-dipper group (4.1 ± 4.0 mL *vs* 4.1 ± 4.7 mL, $P = 0.99$). In the group with higher night-time systolic BP, there was a tendency of increasing WMH volumes in the non-dipper group, but there was no statistical difference (6.4 ± 8.3 mL *vs* 9.7 ± 8.6 mL, $P = 0.14$).

Discussion

The major findings of the present study were that mean night-time systolic BP positively correlated to WMH volumes, and that office BP showed no correlation with WMH volume.

Many studies have shown that circadian BP variation rather than night-time BP is an exacerbating factor of WMH.[17,18] In the results of the present study, dipper-type circadian variation was significantly common in the group with lower night-time BP. In contrast, mean night-time systolic BP was more significantly related to WMH volume than circadian BP variation, and it is assumed that insufficient nocturnal BP decrease might be one major factor that exacerbates WMH. In a recent study, the importance of nocturnal BP has been shown, as it has been reported that high nocturnal BP is associated with an increase in all-cause mortality and cardiovascular events,[20] as well as the onset of chronic kidney disease.[21] Such reports support the present results. We believe that decreasing nocturnal BP is an important part of controlling WMH.

Unfortunately, the nature of the association between lowering nocturnal BP and cerebral blood flow (CBF) is not known. In hypertension, arteriosclerotic changes in the cerebral blood vessels lead to functional alternations in the cerebral microcirculations and limit the autoregulation of CBF through various mechanisms. It has been reported that adequate nocturnal BP decrease was

Table 4 Two-group comparison based on night-time systolic blood pressure

Parameters	NBP < 125 (n = 47)	NBP ≥ 125 (n = 37)	P
Age (years)	69.7 ± 3.6	69.8 ± 3.6	0.96
Male (%)	24 (51.1%)	16 (43.2%)	0.47
Height (cm)	159.4 ± 8.4	155.9 ± 7.4	0.098
Bodyweight (kg)	60.0 ± 10.1	57.2 ± 10.6	0.31
BMI (kg/m^2)	23.5 ± 3.4	23.3 ± 3.4	0.82
Diabetes	7 (14.9%)	7 (18.9%)	0.62
Lipidemia	14 (29.8%)	17 (45.9%)	0.12
Office BP			
Systolic (mmHg)	133.7 ± 12.2	132.0 ± 12.4	0.61
Diastolic (mmHg)	78.3 ± 6.5	75.8 ± 9.9	0.24
HR (b.p.m.)	72.4 ± 12.5	71.2 ± 8.5	0.68
Dipper (%)	30 (63.8)	8 (21.6)	0.0002
IMT (mm)	0.66 ± 0.02	0.71 ± 0.03	0.13
ABI	1.14 ± 0.22	1.14 ± 0.07	0.81
baPWV (cm/s)	1726 ± 273	1858 ± 265	0.07
UA (mg/dL)	5.4 ± 1.1	5.7 ± 1.8	0.45
BUN (mg/dL)	16.7 ± 3.8	16.1 ± 5.7	0.62
Cr (mg/dL)	0.82 ± 0.18	0.78 ± 0.22	0.53
LDL (mg/dL)	113 ± 18	111 ± 31	0.81
HDL (mg/dL)	54 ± 13	57 ± 12	0.41
TG (mg/dL)	150 ± 153	116 ± 49	0.24
glucose (mg/dL)	119 ± 33	116 ± 28	0.69
HbA1c (%)	6.0 ± 0.5	6.1 ± 0.7	0.64

ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; Cr, creatinine; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; HR, heart rate; IMT, intima media thickness; LDL, low-density lipoprotein cholesterol; TG, triglyceride; UA, uric acid; UN, urea nitrogen.

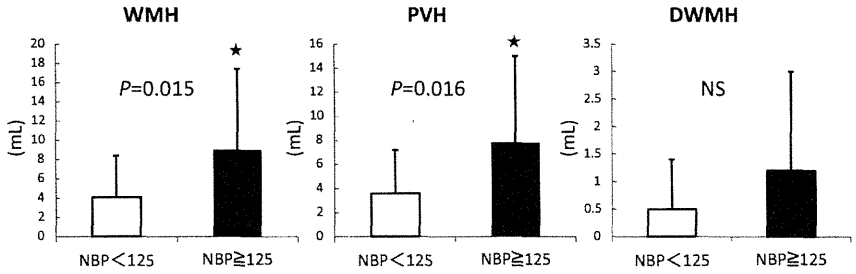

Figure 1 The relationship between night-time mean systolic blood pressure and white matter hyperintensity (WMH) volumes. WMH volume was significantly greater in the group with night-time systolic blood pressure (NBP) ≥125 mmHg than that in the <125 mmHg group, primarily attributed to elevated periventricular hyperintensity (PVH) volumes. DWMH, deep white matter hyperintensity; NS, not significant.

associated with increased CBF in patients with a history of cerebral infarction.[22] Non-dipping of nocturnal BP is associated with increased levels of markers of endothelial dysfunction and inflammation.[23] Taken together, nocturnal BP might be linked to CBF regulation, and lowering nocturnal might may have a favorable impact on cerebral circulation.

To date, no studies have investigated whether lowering nocturnal BP inhibits the progression of WMH. In contrast, very few studies have examined whether the administration of antihypertensive agents prevents the progression of WMH. In the MRI substudy of the PROGRESS trial, 192 patients were given a perindopril-based treatment, as an angiotensin-converting enzyme

inhibitor, with the diuretic indapamide or a placebo.[24] After follow up for 36 months, the volume of new WMH was lower in the treatment group compared with the placebo group. Systolic BP had decreased by a mean of 11.2 mmHg, and diastolic BP had decreased 4.3 mmHg in the treatment group compared with the placebo group. In the Prevention Regimen for Effectively Avoiding Second Stroke study, 771 patients were given antiplatelet agents after cerebral infarction and followed up for approximately 28 months. The patients were divided into a group given additional telmisartan, an angiotensin II receptor blocker, and a group given an additional placebo. There was no significant difference observed in WMH progression between the two groups.[25] Mean BP was just 3.0/1.3 mmHg lower in the treatment group compared with the placebo group. At the present stage, it has been shown that aggressive antihypertensive treatment only inhibits WMH progression. However, both studies evaluated office BP only, and we believe that in the future, BP should be strictly controlled using ABPM to investigate changes in WMH.

Here, we would like to re-emphasize the importance of controlling BP using ABPM as an indicator to control WMH. In the present results, there was no correlation observed between office BP and WMH volume. This is because of the fact that all patients were receiving antihypertensive treatment, and thus in most cases the office BP was well controlled. Therefore, even if the office BP is controlled well, WMH can progress in the event of nocturnal hypertension, or non-dipper type circadian BP variation. Many studies to date have shown that ABPM is a prognostic factor for cardiac, renal, and cerebral disease in middle aged and older people with hypertension.[26] A recent study showed that for elderly individuals, BP measurements obtained by ABPM rather than office BP are a predictive factor of cerebrovascular disease and cognitive decline.[27] Another important point of measuring night-time BP with ABPM is the superior reproducibility compared with other time periods. BP is more variable during the day than during the night because of physical and mental activity. Therefore, we believe that management of WMH should be carried out using ABPM.

The present study had some limitations. First, the details of antihypertensive treatment were an issue. To be specific, many different antihypertensive agents were given, and the number of agents given varied. As the present study was a relatively small-scale cross-sectional study, the effect of each antihypertensive agent could not be examined.

Second, metabolic diseases (diabetes and dyslipidemia) were included. However, as there were no correlations between WMH volume and values for hemoglobin A1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride, we believe that they did not affect the results of our study.

The present study showed that elevated mean night-time systolic blood pressure was a major risk factor for the development and exacerbation of WMH. To prevent the progression of WMH, management by office BP alone is insufficient, and we recommend controlling BP on the basis of ABPM. Further studies are required to determine whether lowering nocturnal blood pressure should be targeted to prevent the progression of WMH.

Acknowledgments

This study was carried out with the support of grants from Research Funding of Longevity Sciences (25-6) from the National Center for Geriatrics and Gerontology (NCGG).

Disclosure statement

The authors declare no conflict of interest.

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The Journal of Frailty & Aging©
Volume 3, Number 3, 2014

ORIGINAL RESEARCH

A NEW GRIP STRENGTH MEASURING DEVICE FOR DETAILED EVALUATION OF MUSCLE CONTRACTION AMONG THE ELDERLY

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Abstract: *Background:* We developed a new grip strength measuring device, which considers the time axis, for evaluating muscle contraction in detail in elderly people. *Objectives:* To present the novel device and preliminary results concerning agility in gripping. *Design:* Cross-sectional analysis. *Participants:* One hundred and twenty-one older persons (48 men and 73 women, mean age 74.4 years) referring for memory disorders to the outpatient clinic of our institute. *Measurements:* A novel device taking advantage of an industrial force-gauge was developed for measuring gripping performance. The instrument graphically described participants' strength production. Nine indices were derived from four points identified by the graph: 1) starting point ("Go signal"), 2) time when gripping starts, 3) turning point (TP) when the inclination of the curve depicting strength production changes, and 4) peak of strength production. Results obtained from the study sample of older persons were compared (as ratios) to a control group of 30 healthy young adults in their thirties in order to calculate age-related decline rates. Differences between right and left side were compared. *Results:* A significant difference was observed between right and left hands concerning the time to reach peak of strength, and time from TP to strength peak in both men and women. For women, the following indices were also significantly different: time to reach TP, strength at TP, time from TP to strength peak, curve inclination from TP to strength peak, and ratio of TP strength divided by peak strength. *Conclusion:* Declines in several indices of gripping agility were measured. The parameters which were more closely related to time than strength itself showed significant differences between right and left hands, especially in women.

Key words: Grip strength, measuring device, detailed evaluation, muscle contraction.

Introduction

In developed countries worldwide, the number of older persons has been constantly growing. Among these countries, Japan is the very first to have gained status as a super-aging society (1). Here, the elderly, and especially the frail population, is rapidly increasing. Sarcopenia is one of the major contributors to frailty (2-4). Recently, the importance of combining muscle strength together with muscle mass has been formally recognized in the operational definition of sarcopenia (5, 6). In parallel, the concept of dynapenia (7-10), a characteristic only considering the muscle production, has also gained special attention.

For the evaluation of muscle strength, the handgrip test is one of the most popular and widely utilized methods (5, 11, 12). It is considered as a general indicator of muscle function (11, 13-15). However, although commonly done in elders, it is still unclear whether an ordinary grip strength device designed for young individuals may be suitable for measuring very weak strength. For example, in nursing home residents (164 women, mean age 83.2 years old), mean values of handgrip strength of 8.7 kg have even been reported (16). Moreover, it has been taken for granted that in measuring grip strength, the maximum (or peak) value (17) during the action of grasping is the sole relevant parameter, probably because it is the only value which can be simply examined by the common dynamometers. Nevertheless, as a matter of fact, there are various ways for expressing grip performance produced from the very beginning to end, such as how the strength increases, peaks, and/or is maintained. Perhaps, even before the start of gripping, useful information might be provided by the reaction time (i.e. how quickly the test is started after the "Go" signal).

In this report, we present a novel device for measuring grip strength developed at our institute. The device can accurately measure very weak peak values, the agility at gripping, the endurance of grip, and the reaction time in the production of the test.

Methods

Study population

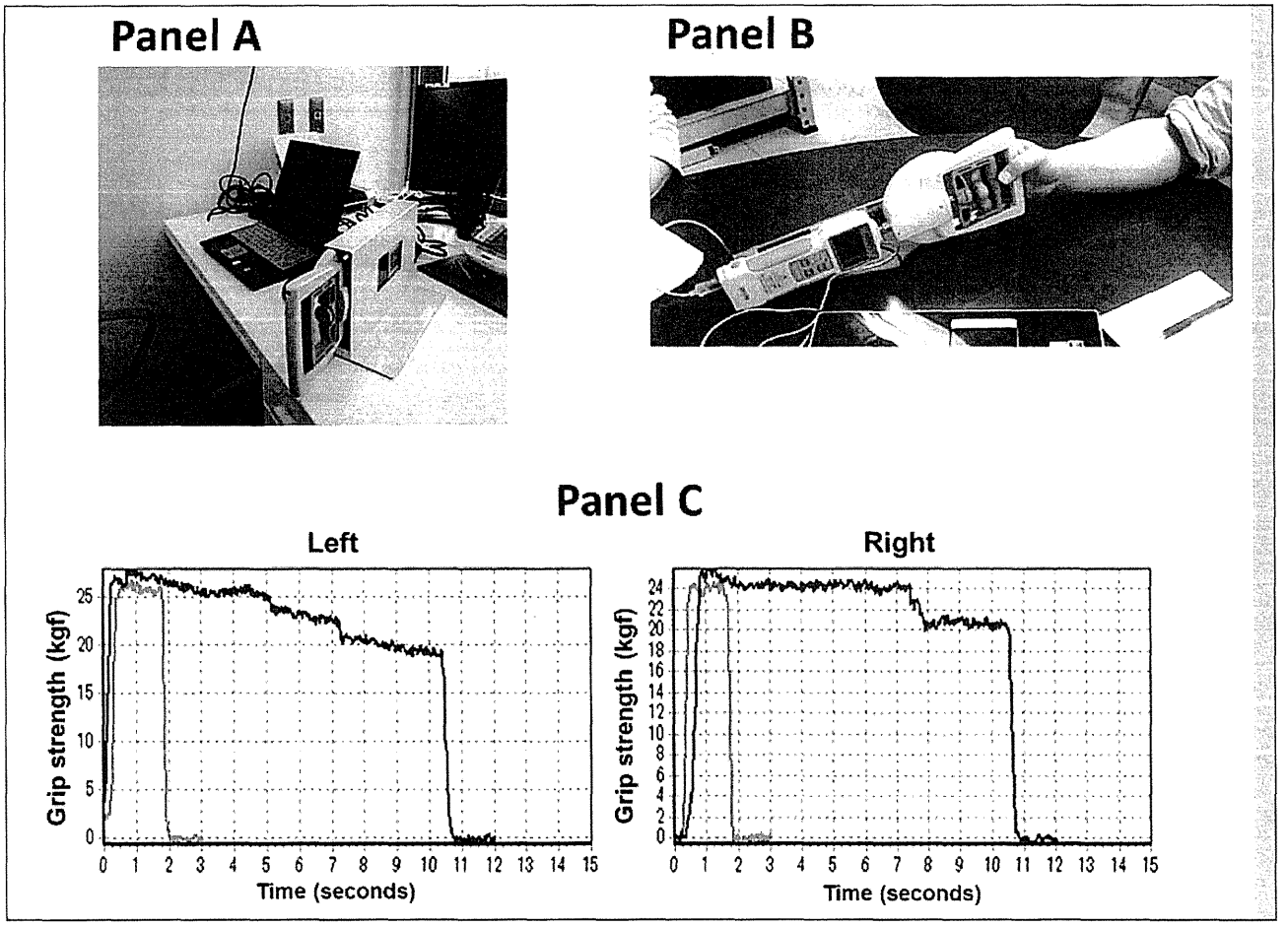
Participants considered in the present analyses were recruited among subjects referring to our outpatient clinic for memory disorders at the National Center for Geriatrics and Gerontology (Obu City, Aichi Prefecture, Japan). The period of recruitment was from October 2010 to March 2011. The inclusion criteria were: 1) first time visit to the clinic, and 2) ability to understand the instructions on how to measure grip strength with the new device. Before the examination, the participants' blood pressure was measured for excluding patients with systolic values higher than 160 mmHg. The local ethical committee approved the study, and participants (or their legal representative) signed an informed consent.

Received June 11, 2013
Accepted for publication November 19, 2013

The Journal of Frailty & Aging©
Volume 3, Number 3, 2014

Figure 1

Panel A: The novel device for measuring grip strength. Panel B: Force-gauge (made by IMADA Co. Ltd, Aichi, Japan) can be used for measuring industrial products. The gauge is equipped with an easy-to-grip handle. Panel C: The output from the device is sent to the computer (pink lines: agility, blue lines: endurance). At the moment the LED light is activated, the subject grips the handle. Grip strength is then constantly recorded by the computer. The way the grip strength is produced is automatically described on the computer monitor



The Novel Device for Measuring Grip Strength

A force-gauge (product No. ZP-500N, IMADA Co. Ltd, Toyohashi, Aichi, Japan) designed for measuring industrial products was incorporated in the novel device provided of a handle for gripping (Figure 1, Panels A and B). The signal output produced by the grip strength of the handle is sent from the device to a computer that constantly record its variations. The way the gripping strength is produced is automatically depicted on the computer monitor (Figure 1, Panel C). The device may thus measure the maximum (peak) grip strength, the reaction time to the "Go" signal, the agility of the individual (at catching the handle), and the endurance (capacity of the individual at maintaining the strength production over time; see also below).

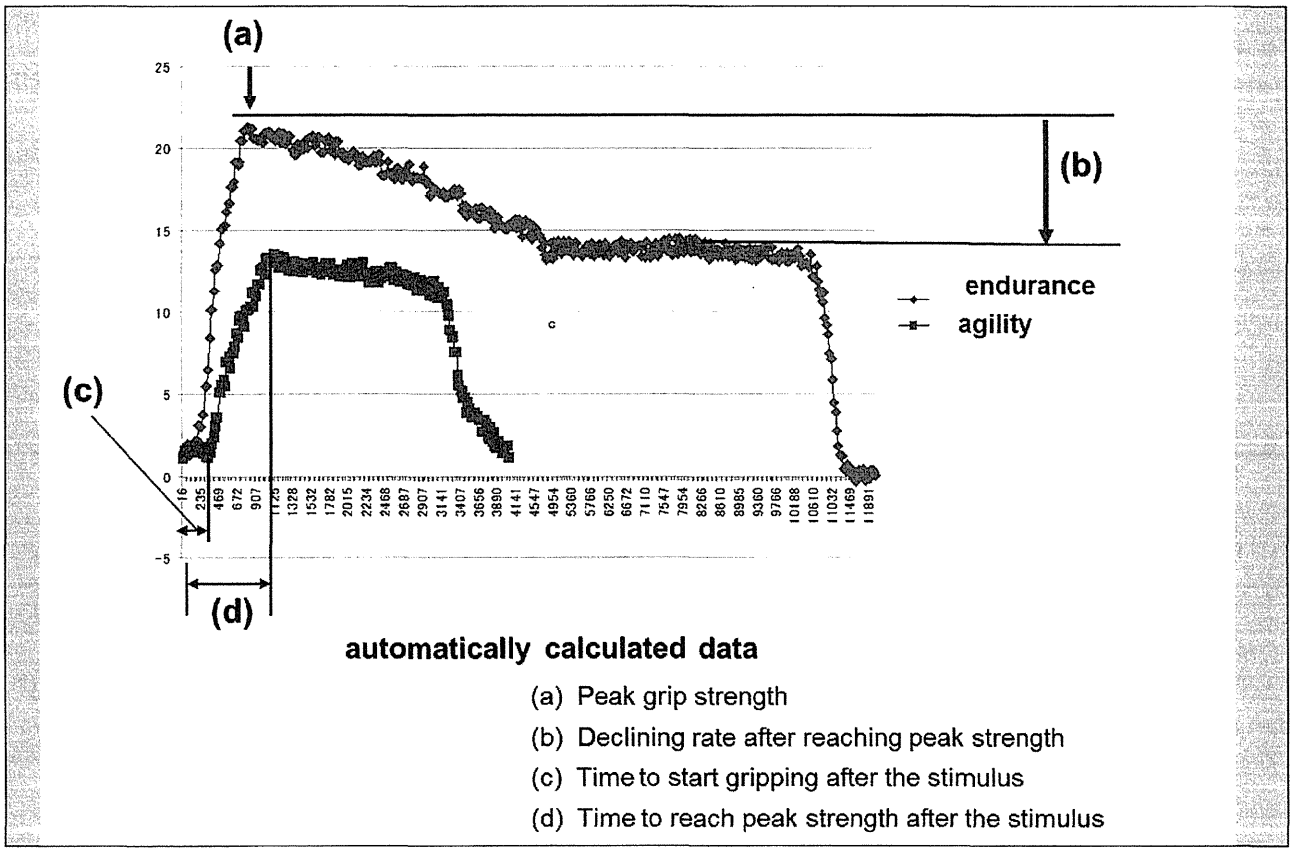
Parameters

Subjects were assessed in a sitting position with their elbows flexed at 90°. In the agility examination, the subject is asked to grip the handle as soon as a LED light (connected to the device) is on. The time and pattern for reaching the peak value of produced grip strength are then measured.

For the endurance examination, the participant is asked to grip the handle as strongly as possible and maintain the effort for up to 10 seconds. The following four parameters are then automatically obtained: a) peak of grip strength, b) declining rate after reaching peak strength, and time to c) start gripping and d) reach the peak strength after the stimulus (LED turning on; Figure 2).

For additional analyses, four points were chosen from the output graph: a) turning on of the LED light ("Go" signal), b)

Figure 2
Graph showing four automatically calculated data on agility and endurance



time to start gripping, c) turning point (TP) when the inclination of the strength production curve changes, and d) peak value of produced strength. From these four points, nine parameters were then calculated (Figure 3): 1) Peak strength, 2) Response time, 3) Time to reach peak strength, 4) Time to reach the TP, 5) Strength at the TP, 6) Inclination from start to the TP, 7) Time from the TP to peak strength, 8) Inclination from the TP to peak strength, and 9) Ratio of strengths (TP divided for peak strength).

Statistical analyses

Men and women were separately analyzed. The mean values of these basic four parameters obtained with the right hand were compared across three different age groups (i.e. <70 years, 70 to 79 years, and 80 years and older). Data were expressed as the decline rates compared to a referent population of healthy young adults in their thirties (14 men and 16 women) working in our Institute. Results are expressed as a percentage of the referent group results. The means of the measured absolute values and the differences in decline between the right and left hands were compared. Statistical significance was set at a p value <0.05. One-way ANOVA tests were performed. SPSS software was used for the present analyses.

Results

Two hundred and twenty-four subjects (84 men and 140 women, mean age 74.8 [standard deviation, SD 8.8] years) were considered for the basic analyses of the automatically calculated data. Secondary analyses on gripping agility were conducted in a subsample of 121 patients (48 men, mean age 73.7 [SD 9.2] years, and 73 women, mean age 74.9 [SD 8.4] years).

Table 1 presents the comparison of the four basic parameters across age groups. The mean peak grip strengths of participants aged <70 years, between 70 and 79 years, and 80 years and older were 24.5 kg, 21.8 kg, and 17.3 kg, respectively. Results for the oldest group were significantly lower than those reported in the other two groups. Mean rates of decline after reaching peak strength were 31.7%, 35.6%, and 39.5% in the three groups, respectively. The rate of the oldest group was significantly steeper than in the lowest age group. As for agility, the mean times to start gripping after the "Go" signal were 0.33 seconds, 0.44 seconds, and 0.47 seconds in the three

Table 1
Comparison of four basic parameters across three age groups

Age groups	Peak strength (kg)	Declining rate after reachingpeak strength (%)	Time to start gripping after light on (sec)	Time to reach peak strength after light on (sec)
a. <70 years old (n=53, Men 23, Women 30)	24.5 ± 8.2 [c]	31.7 ± 14.1 [c]	0.33 ± 0.18 [c]	1.39 ± 0.58 [b,c]
b. 70-79 years old (n=92, Men 39, Women 53)	21.8 ± 8.5 [c]	35.6 ± 19.2	0.44 ± 0.31	1.71 ± 0.62 [a]
c. 80 years and older (n=79, Men 22, Women 57)	17.3 ± 7.5 [a,b]	39.5 ± 19.3 [a]	0.47 ± 0.36 [a]	1.77 ± 0.65 [a]

Results are presented as means ± SD. Superscript letters represent statistically significant differences ($p<0.05$) of the single parameters across age groups.

Table 2
Mean values of the nine parameters of interest

	Men		Women	
	Right	Left	Right	Left
(1) Peak strength (kg)	26.3 ± 8.7	24.7 ± 8.2	18.1 ± 7.0	16.9 ± 7.2
(2) Response time (ms)	383.1 ± 165.0	360.3 ± 129.8	408.9 ± 171.1	366.6 ± 142.5
(3) Time to reach peak strength (ms)	1310.2 ± 401.8	1225.9 ± 418.6	1273.3 ± 410.2	1204.4 ± 420.5
(4) Time to reach the TP (ms)	737.9 ± 261.2	671.5 ± 202.6	734.6 ± 257.4	680.9 ± 244.4
(5) Strength at the TP (kg)	22.3 ± 8.1	20.5 ± 7.6	14.9 ± 6.5	13.8 ± 6.2
(6) Inclination from start to the TP (kg/ms)	0.068 ± 0.038	0.068 ± 0.037	0.046 ± 0.029	0.044 ± 0.026
(7) Time from the TP to peak strength (ms)	572.3 ± 381.6	554.5 ± 337.3	538.7 ± 338.0	523.5 ± 335.2
(8) Inclination from the TP to peak strength (kg/ms)	0.010 ± 0.009	0.011 ± 0.011	0.007 ± 0.006	0.008 ± 0.006
(9) Ratio of TP strength/peak strength (%)	84.2 ± 10.5	82.5 ± 10.7	81.7 ± 12.2	81.2 ± 12.3

Results are presented as means ± SD. TP: turning point.

Table 3
Comparisons of age-related decline rates of the nine parameters of interest according to gender and right/left hand

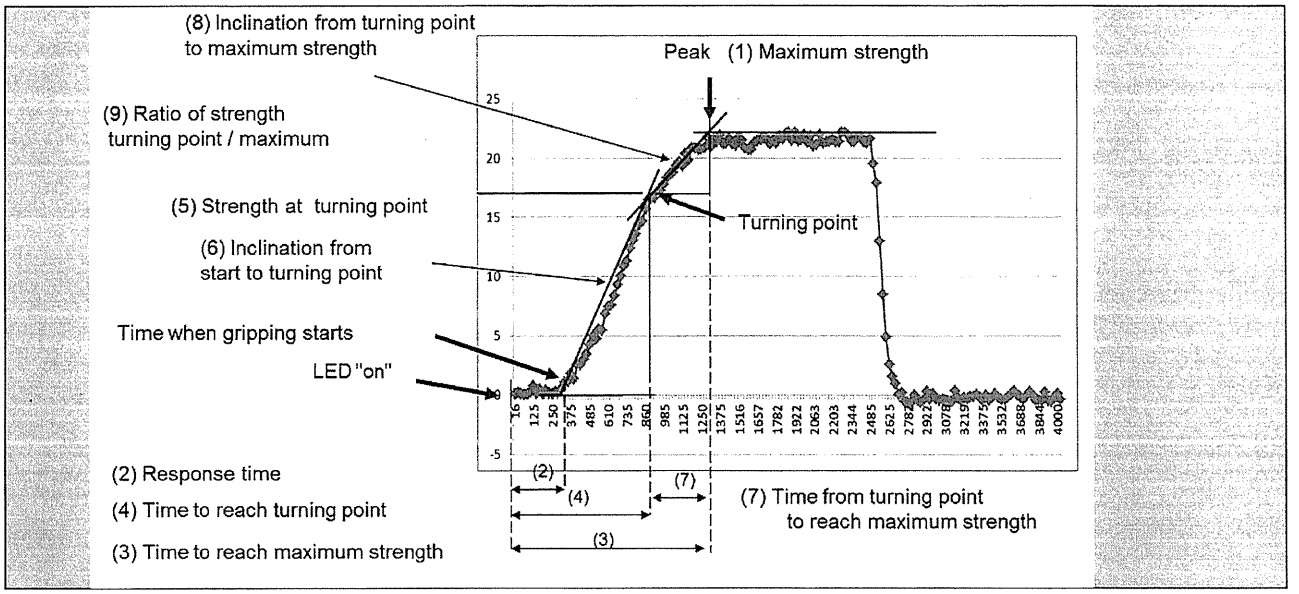
	Men			Women		
	Right	Left	p	Right	Left	p
(1) Peak strength (kg)	-61.9	-60.6	0.36	-66.7	-66.3	0.78
(2) Response time (ms)	+167.4	+159.8	0.38	+178.2	+173.7	0.59
(3) Time to reach peak strength (ms)	+122.1	+135.9	0.02	+139.0	+149.8	0.04
(4) Time to reach the TP (ms)	+173.0	+161.7	0.19	+179.9	+152.9	<0.01
(5) Strength at the TP (kg)	-63.4	-60.7	0.15	-70.2	-62.3	<0.01
(6) Inclination from start to the TP (kg/ms)	-38.9	-39.3	0.84	-37.0	-39.8	0.09
(7) Time from the TP to peak strength (ms)	+88.5	+114.0	0.01	+106.1	+146.0	<0.01
(8) Inclination from the TP to peak strength (kg/ms)	-84.5	-64.9	0.11	-44.8	-60.0	<0.01
(9) Ratio of TP strength/peak strength (%)	+101.0	+99.3	0.44	+103.6	+93.0	<0.01

Results are presented as percent change of the sample group compared to a referent group of young healthy individuals. TP: turning point.

groups, respectively. Again, the time of youngest group was significantly lower compared to the other two groups. Finally, the mean times to reach peak strength after the "Go" signal were 1.39 seconds, 1.71 seconds, and 1.77 seconds in the three groups, respectively. The time of the youngest group was significantly lower compared to the other two groups.

The mean values of nine additional parameters are shown in Table 2. When right and left hands were compared for rates of decline against young healthy controls, significant differences were observed between the right and left hand for 1) time to

Figure 3
Graph showing the nine parameters for the agility examination



reach the peak strength, and 2) time from the TP to peak, in both men and women. The following indices were also significantly different in women: a) time to reach the TP, b) strength at the TP, c) inclination from the TP to peak, and d) ratio of values of the TP compared to peak (Table 3). In men, the difference in rates of decline between right and left hands occurred only after the TP, whereas in women it occurred both before and after the TP.

Discussion

In the present paper, we have presented a novel grip strength measuring device, particularly suitable for the assessment of frail older persons. The device specially considers the generated strength over a time axis. It can accurately measure small values, and also record additional parameters related to muscle contraction (e.g., agility or catching ability; response time; endurance or holding ability). Our results show the time and way the peak values are reached, then the subsequent declines occurring over a short period of time (10 seconds). The proposed novel indices were then compares across different age groups and right/left hands in older persons.

Although our results are to be considered as preliminary, the declines of the described parameters (both in agility and endurance) may still have some relevance in terms of pathophysiology of aging. Furthermore, differences in the decline of agility between right and left hand were observed. Interestingly, both genders presented a marked decline after the turning point of the curve during the grip strength augmentation for reaching the peak value. After the turning point, decline was particularly evident in the left hand. At the same time, women showed a significant different decline between right and left side also before the turning point, with more evident decline observed at right hand. Since this kind of comparison between right and left hands has rarely been done so far, we cannot compare with previous studies. Hence, the validity of the results, the underlying mechanisms and the implied effects warrant further investigation.

One may wonder whether the turning point is always present or not. It seems that when the subject's grip strength is very strong, the strength production reaches its peak so rapidly that the turning point becomes less evident. Differently, the turning point becomes more clearly when the individual's muscle strength is relatively weak. In any case, what a turning point signifies in the physiological (or pathological) states during muscle contraction is also an interesting target for ongoing and future research. It might be speculated that it may derive from the proportional change between fast- and slow-twitch fibers, or from the shift of effort between the contracting flexor and extensor muscles. Further studies using electromyography examinations in combination with our device might answer to such issue. Interestingly, our findings reveal significant differences of muscle activity more related to time than to strength.

In the process of advancing frailty, the gradual decline in muscle strength is likely be accompanied by reduction in agility or endurance of muscle contraction. However, there is not a widely diffused and simple method to adequately evaluate these parameters (18, 19). Our novel device, thanks to its fine technological advances already adopted in industry, can safely provide such information.

Some limitations of the present study need to be presented.

First, its cross-sectional design does not allow any speculation about causal-effect mechanisms. Moreover, the study sample (from patients referred to an outpatient memory clinic) may not be representative of larger populations. Nevertheless, the inner nature of our analyses is not affected but this possible issue. A major limitation is represented by the lack of a reference measure to which comparing our findings. The relatively novel identification of the turning point and the lack of simultaneous assessment to verify its presence (for example electromyography exam), further studies are needed to confirm its presence and value. Right in these days, we are investigating the significance of the turning point by correlating it with specific clinical parameters. Another issue may be represented by the cognitive impairment affecting the studied population. This might have affected some of our results in terms of reflexes and/or capacity to correctly perform the test. In addition to these points, we do not compare true dominance and non-dominance, although the average rate of left-handed dominance is known to be about 10% in Japanese people (20).

In conclusion, time-related parameters of muscle function show significant differences between right and left hands, particularly in women. The novel grip strength device proposed in this paper may represent a useful addition for future studies on frailty and sarcopenia.

Acknowledgements: This work was supported by The Research Funding for Longevity Sciences (23-24) from the National Center for Geriatrics and Gerontology (NCGG), Japan. We thank the BioBank, NCGG for quality control of clinical data.

Conflict of Interest: None.

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JAMDA 15 (2014) 36–41

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JAMDA

journal homepage: www.jamda.com

Original Study

Regional White Matter Lesions Predict Falls in Patients With Amnestic Mild Cognitive Impairment and Alzheimer's Disease

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Keywords:
White matter lesions
falls
amnestic mild cognitive impairment
Alzheimer's disease

A B S T R A C T

Objectives: Preventive strategy for falls in demented elderly is a clinical challenge. From early-stage of Alzheimer's disease (AD), patients show impaired balance and gait. The purpose of this study is to determine whether regional white matter lesions (WMLs) can predict balance/gait disturbance and falls in elderly with amnestic mild cognitive impairment (aMCI) or AD.

Design: Cross-sectional.

Settings: Hospital out-patient clinic.

Participants: One hundred sixty-three patients diagnosed with aMCI or AD were classified into groups having experienced falls (n = 63) or not (n = 100) in the previous year.

Measurements: Cognition, depression, behavior and psychological symptoms of dementia, medication, and balance/gait function were evaluated. Regional WMLs were visually analyzed as periventricular hyperintensity in frontal caps, bands, and occipital caps, and as deep white matter hyperintensity in frontal, parietal, temporal, and occipital lobes, basal ganglia, thalamus, and brain stem. Brain atrophy was linearly measured.

Results: The fallers had a greater volume of WMLs and their posture/gait performance tended to be worse than nonfallers. Several WMLs in particular brain regions were closely associated with balance and gait impairment. Besides polypharmacy, periventricular hyperintensity in frontal caps and occipital WMLs were strong predictors for falls, even after potential risk factors for falls were considered.

Conclusions: Regional white matter burden, independent of cognitive decline, correlates with balance/gait disturbance and predicts falls in elderly with aMCI and AD. Careful insight into regional WMLs on brain magnetic resonance may greatly help to diagnose demented elderly with a higher risk of falls.

The incidence of falls increases with age. Falls often cause fractures, disability, and injury-related death. Even if falls are not accompanied by fractures, the elderly are reluctant to be active for fear of falls.[1] In Japan, a super-aged society, falls have become not only a medical problem, but also a social and medico-economic concern.

Falls are induced by the interaction of intrinsic, pharmacologic, and environmental factors in older persons. Intrinsic risks include balance impairments and muscle weakness, which are caused by a number of sensory, neurologic, depressive, or musculoskeletal diseases. Age-related physical changes, medications, and cognitive decline also affect gait function in the elderly.[2,3] Although gait impairment is not typically seen early in the course of Alzheimer's disease (AD), patients with AD show balance impairment and a slower walking pace, and the incidence of falls in this population is approximately 3-fold higher than that of age-matched controls.[2,4] Clinical features of AD might play a role in increasing falls in the early stages of the disease. The involvement of executive dysfunction, visuoconstructional deficits, and behavior and psychological symptoms of dementia (BPSD) has been suggested.[5,6] Another factor accounting for impaired balance and gait could be the underlying burden of white matter lesions (WMLs) in AD patients.

Previous studies of the aging brain have reported the correlation of WMLs with measurements of balance, gait, and falls in the elderly.[7–14] Frontotemporal cortex and periventricular white matter are particularly vulnerable to hypoperfusion, and WMLs in these

This work was supported by the research fund for Longevity Sciences (22-5, 25-5) from the National Center for Geriatrics and Gerontology, Japan and Health and Labor Sciences Research Grants (H21-choju-005, H25-Ninchisho-008).

The authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.jamda.2013.11.004

structures could have the consequence of impaired balance and gait in the elderly.[14] However, little is known about the interaction between WMLs and gait disturbance in dementia disorders.[7,8]

The purpose of the present study is to clarify the effects of WMLs on balance/gait function and falls in patients with amnestic mild cognitive impairment (aMCI) and AD. In the present study, we hypothesized that white matter burden (both its location and volume) is critical for manifesting clinical symptoms. We investigated the features of regional distribution of WMLs, which are responsible for deterioration of posture control and gait. Finally, we aimed to determine whether regional WMLs could be predictive to find high risk individuals for falls among elderly with aMCI and AD.

Methods

Participants

The protocol of the study was approved by the Institutional Review Board of the National Center for Geriatrics and Gerontology (NCGG), Japan. Candidate patients and their caregivers submitted informed consent before participation in the study.

We enrolled 163 patients (111 females) consecutively. Patients were >65 years old, visited the NCGG hospital in 2010 and 2011, and were diagnosed with aMCI ($n = 14$) or AD ($n = 149$). Patients were classified into a group that had experienced falls (fallers group; 63 subjects) and a group that had not experienced falls (nonfallers group; 100 subjects) in the past year. Mild to moderate AD was diagnosed as possible or probable AD according to the criteria from the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association,[15] and their total Mini-Mental State Examination (MMSE) scores were 15 or over. Patients with aMCI were diagnosed based on the criteria defined by Petersen et al.[16] Patients with severe conditions of cardiac failure, renal disorder, liver dysfunction, musculoskeletal disease, optic or neurological disorders other than AD, and patients with a history of stroke or cortical lesions on brain magnetic resonance (MR) imaging were excluded.

Evaluation of Fall Risk Factors

Experience of falls was ascertained by interviews with patients and their caregivers. Risk of falls was evaluated by the Fall Risk Index, comprising 21 questionnaires for physical function, geriatric syndrome, and environmental hazards.[17] The presence or absence of knee joint pain was examined as a subitem of the FRI. Information about previous history and medication was obtained from the patients' clinical charts. Polypharmacy was defined as taking 5 or more types of oral medicine.[18] The patient's drinking habit was assessed by 1 of the questionnaires on a 4-point scale (0: daily drinking ≥56 g ethanol, 1: daily drinking <56 g ethanol, 2: occasional drinking, 3: none). Anemia was assumed to be present if the patient's hemoglobin was less than 11.0 g/dL.

Cognitive function was evaluated by MMSE, Alzheimer's Disease Assessment Scale (ADAS), and digit span.[19,20] Depression and BPSD were estimated by the Geriatric Depression Scale-15 and Dementia Behavior Disturbance Scale, respectively.[21,22]

Balance control was assessed from the center of gravity sway during 1 minute of standing on a stabilometer (Stabilometry analysis SYSTEM GP-5000; ANIMA Co., Tokyo, Japan) with eyes opened and closed. Parameters of the postural sway included enveloped area (ENV-AREA), which is an area inside of the envelope of the center of gravity sway, total trajectory length of traced sway (LNG), and trajectory length of X direction (X-LNG) and Y direction (Y-LNG), which measure the length from displacement of sway in mediolateral and anteroposterior directions, respectively.

Gait function was evaluated by the Timed Up and Go test (TUG), tandem gait steps, and time of standing on one leg. Muscle strength was measured by a hand grip test.

Brain MR Imaging

A standard series of axial T1-weighted (repetition time [TR], 485 ms; echo time [TE], 11 ms), T2-weighted (TR, 3800 ms; TE, 93 ms) and fluid-attenuated inversion recovery (TR, 8000 ms; TE 101 ms; inversion time, 2500 ms; a 256 × 256 matrix) MR sequences of the brain were performed using 1.5 T MR scanner (Siemens Avanto, Munich, Germany). Scans in parallel with the anterior commissure-posterior commissure line were performed from the vertex to the foramen magnum with 6-mm thick slices and an interslice gap of 1.2 mm.

Rating of WMLs and Brain Atrophy

WMLs appeared as hyperintense on T2-weighted images but did not leave a clear hypointense hole on T1-weighted images. WMLs were visually assessed as periventricular hyperintensity (PVH) or deep white matter hyperintensity (DWMH). WMLs were considered periventricular if the largest diameter was adjacent to the ventricular lining; they were otherwise considered subcortical.[23] PVH was classified by a 5-point scale measured at frontal caps, wall of the lateral ventricle (bands), and occipital caps (0: no, 1: pencil thin lining <3 mm, 2: smooth halo or thick lining 3–10 mm, 3: extending caps 10–25 mm, 4: large confluent white matter >25 mm). The overall degree of PVH was calculated by adding up the scores for the 3 separate compartments.[23] The number and size of DWMH were counted in the frontal, parietal, temporal, and occipital lobes, basal ganglia, thalamus, and brain stem. The size of DWMH was classified according to the largest diameter: small (1–3 mm), medium (3–10 mm), or large (>10 mm). To calculate the volume, DWMH was assumed to be spherical with a fixed diameter of 2, 6, and 12 mm for each of the 3 respective categories.[23]

For analysis of brain atrophy, Evans ratio (ER), inverse cella media index (iCMI), caudate head index (CHI), and basal cistern index (BCI) were calculated.[23] The following were measured with slide calipers: the maximum distance between the tips of the anterior horns (A); the width between the bilateral heads of the caudate nuclei (B); the maximum transverse inner diameter of the intracranial space (C); the maximum width of the cella media (D); the maximum transverse inner diameter (E); the internal width between the bilateral temporal lobe (F); and the maximum transverse inner diameter (G). The ER, iCMI, CHI, and BCI were calculated with the following respective formulae: ER = A/C; iCMI = D/E; CHI = B/C; and BCI = F/G, respectively.

WMLs in all participants were collectively evaluated by 2 trained raters, who had no knowledge of the clinical data. To test the inter-rater reliability, the results of the 2 raters were subjected to correlation analysis for comparison in a random sample of 10 subjects. The analysis showed a strong correlation ($r = 0.87–0.91$, $P < .0001$), which suggested that the method of measurement used for this study was reliable.

Statistical Analysis

Statistical analysis was performed using SPSS 18.0 for Windows (SPSS Inc, Chicago, IL). Since WMLs did not show normal distribution, they were converted to rank variables and analyzed by nonparametric tests. Clinical information and results of neuropsychological tests, posture sway, and gait were compared between the fallers and the nonfallers by Mann–Whitney U-test. Association between WMLs and balance/gait functions was analyzed by partial Spearman rank order correlation analysis. Independent risk factors of falls were

Table 1
Clinical Characteristics

	Fallers (n = 63)	Nonfallers (n = 100)	*P* Value
Age, years	78.6 (4.9)	76.4 (5.9)	.020
Females, n (%)	45 (71.4)	68 (68.0)	.644
Education, years	10.4 (2.5)	10.5 (2.4)	.713
Polypharmacy, n (%)	27 (42.9)	21 (21.0)	.003
Dementia Behavior Disturbance Scale	18.9 (11.1)	15.1 (10.8)	.013
Geriatric Depression Scale	5.0 (2.4)	3.9 (2.9)	.008
Fall Risk Index	9.0 (2.3)	2.5 (2.1)	<.001
Mini-Mental State Examination	21.1 (3.9)	20.9 (3.6)	.709
Alzheimer's Disease Assessment Scale	16.7 (6.0)	16.2 (6.2)	.659

SD, standard deviation.
Data are presented as mean (SD) unless otherwise indicated.

analyzed by the multivariate logistic regression, and prediction of falls was tested by receiver operating characteristic analysis. Significance was considered at $P < .05$.

Results

Clinical Characteristics and Balance/Gait Performance

The subjects in the fallers group were older than the nonfallers (Table 1). The percentage of patients on polypharmacy was higher in the fallers group. The fallers group had higher total scores of BPSD and depression. Total score of FRI was elevated in the fallers, while environmental factors were not different (data not shown). The prevalence of hypertension, diabetes mellitus, heart disease, anemia, and knee joint pain as well as drinking habit and use of psychotropic medicine were not significantly different among the groups (data not shown). Concerning cognitive status, there was no difference between the groups in terms of performance of MMSE and ADAS, as well as performance of constructional praxis in a subscale of ADAS and digit span, an indicator of attention (data not shown).

Among measurements with the stabilometer, ENV-AREA was enlarged in the fallers compared with the nonfallers with eyes opened or closed (Table 2). In gait performance, the number of steps in tandem gait was significantly fewer in the fallers, whereas results of TUG tended to be worse in the fallers. There was no difference in the grip strength between the groups.

Regional WMLs and Brain Atrophy

The PVH total score and overall products of DWMH were significantly higher in the fallers (Table 3). This group showed higher PVH in frontal caps and occipital caps, and higher DWMH in all regions measured except the brain stem. Concerning progression of brain atrophy, inverse cella media index increased in the fallers, whereas the other indices were unchanged.

Table 2
Balance and Gait Performance

		Fallers	Nonfallers	*P* Value
Measurements of balance				
ENV-AREA, cm^2	Eyes open	6.0 (3.4)	4.7 (2.3)	.032
LNG, cm		121.6 (39.4)	113.5 (39.5)	.185
X-LNG, cm		77.4 (24.3)	70.3 (25.0)	.062
Y-LNG, cm		76.4 (29.0)	74.2 (29.3)	.540
ENV-AREA, cm^2	Eyes closed	8.9 (5.4)	7.1 (4.3)	.017
LNG, cm		172.8 (58.5)	163.0 (73.6)	.117
X-LNG, cm		107.1 (33.7)	99.5 (44.9)	.052
Y-LNG, cm		112.0 (44.8)	108.3 (53.9)	.303
Gait performance				
Timed Up and Go, s		11.4 (4.0)	10.6 (3.0)	.077
Tandem gait, steps		11.4 (7.1)	14.2 (6.9)	.021
One-leg stand, s		26.7 (28.7)	32.8 (33.5)	.177
Grip strength, kg		20.0 (7.5)	22.2 (8.5)	.151

ENV-AREA, enveloped area of the center of gravity sway; LNG, total trajectory length of traced sway; SD, standard deviation; X-LNG, trajectory length of X direction; Y-LNG, trajectory length of Y direction.
Data are presented as mean (SD).

Table 3
Regional WMLs and Brain Atrophy

	Fallers	Nonfallers	*P* Value
PVH			
Frontal caps	4.4 (1.0)	3.6 (1.0)	<.001
Bands	3.1 (1.0)	2.9 (0.9)	.302
Occipital caps	4.5 (1.4)	3.5 (1.4)	<.001
Total	12.0 (2.6)	10.0 (2.8)	<.001
DWMH, μL			
Frontal	2179.4 (1967.1)	1606.6 (1582.3)	.023
Parietal	878.2 (867.5)	700.7 (845.9)	.031
Temporal	273.4 (281.2)	160.8 (188.8)	.007
Occipital	193.7 (217.2)	93.1 (97.1)	<.001
Basal ganglia	354.7 (365.8)	252.8 (303.7)	.026
Thalamus	177.5 (202.2)	124.2 (157.3)	.011
Brain stem	220.0 (228.9)	170.2 (173.6)	.100
Total	4277.0 (3143.3)	3108.4 (2765.2)	.005
Atrophy			
Evans ratio	0.27 (0.04)	0.27 (0.03)	.813
Caudate head index	0.16 (0.03)	0.16 (0.02)	.567
Inverse cella media index	0.24 (0.04)	0.22 (0.03)	.018
Basal cistern index	0.20 (0.02)	0.20 (0.03)	.865

DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity; SD, standard deviation; WML, white matter lesion.
Data are presented as mean (SD).

Correlation of WMLs With Balance/Gait Function

Figure 1 summarizes the correlation between WMLs and posture control for the entire cohort. Absolute values of the partial Spearman rank order correlation after adjusting for age, sex, and MMSE are shown on the Y-axes. PVH total, as well as PVH frontal and occipital caps correlated with Y-LNG with eyes opened ($P = .008$, $P = .019$, and $P = .011$, respectively) and with eyes closed ($P = .015$, $P = .042$, and $P = .044$, respectively). Total PVH also correlated with LNG with eyes closed ($P = .049$). Total DWMH and parietal DWMH correlated with Y-LNG with eyes closed ($P = .032$ and $P = .013$, respectively). Temporal DWMH correlated with Y-LNG with eyes open ($P = .013$), and DWMH in basal ganglia correlated with eyes-closed ENV-AREA ($P = .019$).

Similarly, correlation of WMLs with gait performance was demonstrated (Figure 2). PVH scores at frontal caps, bands, occipital caps, as well as PVH total correlated with performance of TUG ($P = .005$, $P = .001$, $P = .013$, and $P < .001$, respectively). PVH in frontal caps also correlated with 1-leg standing time ($P = .007$). Frontal DWMH and temporal DWMH correlated with performance of 1-leg standing and TUG ($P = .040$ and $P = .030$, respectively). In contrast, muscle strength did not show any correlation with WMLs. Caudate head index was negatively correlated with 1-leg standing ($P = .008$), but no other correlation was found between brain atrophy and balance/gait function.

Association of WMLs With Previous History of Falls

The effect of regional WMLs on falls was tested by multivariate logistic regression (Table 4). Cofactors included age, sex, MMSE, polypharmacy, Dementia Behavior Disturbance Scale, Geriatric Depression Scale-15, and brain atrophy. The analysis indicated that polypharmacy, PVH frontal caps, and occipital DWMH were specific risk factors for falls. The predicted probabilities for fallers from the multivariate logistic regression analysis were as follows: $\text{Log } p/(1\text{-}p) = -0.0534x1 + 0.0282x2 + 0.0948x3 + 0.0140x4 + 0.0852x5 + 0.0069x6 + 0.0061x7 + 0.0004x8 + 0.0130x9 + 0.0041x10 +$