Geriatrics Gerontology International Medline Indexed

Validation of a simple and reliable visual rating scale of white matter hyperintensity comparable with computer-based volumetric analysis

Dear Editor,

White matter hyperintensity (WMH), which is detected as hyperintense signals on T2-weighted images of brain magnetic resonance imaging (MRI), is a common finding in the aging brain. WMH is associated with various geriatric conditions,[1] and regional WMH has specific effects on cognitive impairment, gait and lower urinary tract symptoms.[2–4] To measure WMH, visual rating and volumetric analysis using a computer program have been used. Volumetric measurement of WMH is more sensitive and accurate than visual rating, although the former requires specific laboratory instruments to analyze WMH. Visual rating is time-consuming, and the results often vary among raters. Because physicians have to evaluate longitudinal changes in WMH in patients during a limited consultation time, an easier and more reliable method of visual assessment is required. WMH can be divided into two parts; periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH). Previous studies suggested that PVH and DWMH largely share common pathological characteristics.[5] Automatic segmentation of WMH mostly recognized DWMH in continuity with PVH, and therefore the volume of DWMH is much smaller.[4] Thus, we hypothesized that semiquantitative analysis of PVH could predict total WMH volume. The purpose of the present study was to validate the accuracy of our newly developed visual rating scale for global and regional analysis of WMH. Comparison with conventional methods was carried out by referencing computational volumetric analysis.

The participants were 460 patients (318 women) aged 65–85 years; 69 diagnosed with amnestic mild cognitive impairment and 391 with Alzheimer's disease. Clinical data were obtained from the Biobank of National Center for Geriatrics and Gerontology, which collects clinical data for research. All participants underwent brain MRI. The protocol of brain MRI is described elsewhere.[4] WMH on brain MRI was evaluated by both visual and computational volumetric analysis. For visual rating, we used the Fazekas scale,[6] a scale used in the Rotterdam scan study (Rotterdam scale)[7] and our new scale, which is a modified version of the Rotterdam scale (modified Rotterdam scale).[2,3] The Fazekas scale is a simple classification of PVH (grade 0–3), whereas the Rotterdam scale and modified Rotterdam scale are semiquantitative methods. PVH in the Rotterdam scale is visually rated into four grades at frontal caps, bands and occipital caps. The total score was calculated by adding the three region-specific scores.[7] In contrast, the modified Rotterdam scale rates PVH as five grades with definitive ranges of WMH dimension from the edge of ventricles at the identical regions of PVH, but separately in the left and right hemisphere. The degree of PVH was calculated by adding up the scores of six separate regions.[2,3] Details of each scale are described in the supplemental information. Automatic segmentation of WMH was carried out using Software for Neuro-Image Processing in Experimental Research (SNIPER).[8] SNIPER was used to determine the intracranial volume (IC) and WMH volume in each brain lobe (frontal, parietal, temporal and occipital lobes). WMH volume divided by IC (WMH/IC), to adjust for brain size, was used as an index of WMH. All analyses were carried out using the Japanese version of SPSS for Windows version 22.0 (IBM Corporation, Armonk, NY, USA). Pearson's correlation analysis was used to analyze the association between visual scales and WMH/IC.

Figure 1a shows the distribution of the three rating scales and WMH/IC with box and whisker plots. The three visual rating scales strongly correlated with SNIPER value (WMH/IC; %). The correlation coefficient was 0.820 for all three scales; however, deviation increased with WMH progression, although it was smaller with the modified Rotterdam scale than with the other scales. As the correlation of visual rating and WMH/IC did not seem to be linear, the association of WMH with cubed values of the visual rating scales was examined (Fig. 1b). With cubed values, we were able to find a clear linear association between visual ratings and WMH/IC, with a correlation coefficient of 0.862 and 0.879 for the Rotterdam scale and modified Rotterdam scale, respectively. Finally, the correlation between the visual rating of PVH at frontal caps and frontal WMH/IC was tested. As a result, the cubed score of frontal caps was strongly correlated with WMH/IC in the frontal lobe ($r = 0.827$; Fig. 1c).

The present study found that cubed values of our modified Rotterdam scale showed a good correlation with WMH/IC, with smaller deviation. In addition, the visual rating of PVH at frontal caps correlated with frontal WMH/IC. Several strengths and limitations of the modified Rotterdam scale should be mentioned. First, it requires PVH evaluation only, which is simple and not time-consuming. Therefore, it is easily

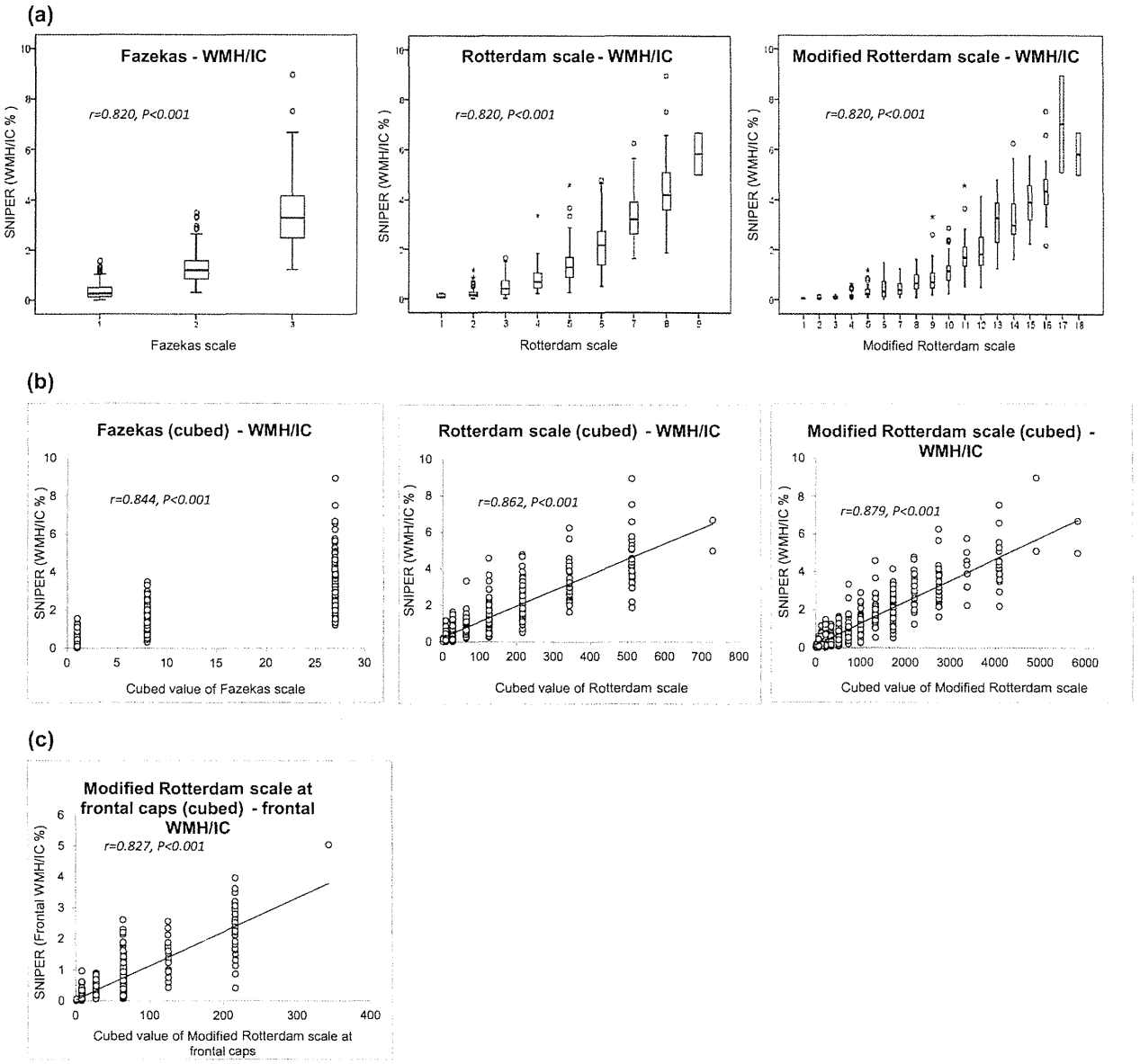

Figure 1 Associations of three visual rating scales with computer-based volumetric analysis. (a) The distribution of the three rating scales and white matter hyperintensity (WMH)/intracranial volume (IC) with box and whisker plots. The *x*-axes are original values of the three visual rating scales. The visual rating scales were strongly correlated with WMH/IC, but the deviation increased with WMH progression. We transformed each WMH/IC (%) value to a z-score for standardization. As a reference, we used the Fazekas scale (grade 1–3), and the Rotterdam scale and modified Rotterdam scale were classified into the three corresponding grades. Then, we compared the difference of deviation of z-score in each Fazekas grade. In the highest Fazekas group (grade 3), a standard deviation of standardized WMH/IC (%) was 0.95. Standard deviation of the Rotterdam scale and modified Rotterdam scale was 0.78 and 0.73, respectively. We analyzed significant difference using the *F*-test, which showed that modified the Rotterdam scale had the smallest deviation ($P = 0.001$). (b) The association between cubed values of the three visual scales and Software for Neuro-Image Processing in Experimental Research (SNIPER; WMH/IC). The *x*-axes denote cubed values of the three visual rating scales. A linear association of WMH/IC with the Rotterdam scale and modified Rotterdam scale is observed. (c) The correlation between cubed values of the modified Rotterdam scale at frontal caps and SNIPER (frontal WMH/IC). The cubed score of PVH at frontal caps was strongly correlated with WMH/IC in the frontal lobe.

applicable in clinical practice. Second, the cubed PVH scale was strongly correlated with total and regional WMH/IC in a linear manner, which enables us to follow longitudinal changes in WMH. In contrast, our scale might not be useful in patients with extensive DWMH lesions. In this connection, automatic segmentation of WMH mostly recognized DWMH in continuity with PVH. Visual differentiation of PVH and DWMH in each MRI slice might be difficult unless 3-D continuity of WMH is apparent. It is suggested that classification of

PVH and DWMH is arbitrary, and causal factors for PVH and DWMH are merely a reflection of total WMH volume.[5] Recently, specific impacts of frontal WMH have been reported.[3,4] Not only the overall presence of WMH in the brain, but also the size and local distribution of WMH might directly cause several clinical symptoms. The modified Rotterdam scale showed the strongest association with frontal WMH/IC, which implies it is a more useful index than the other visual rating scales. Because WMH in bands and occipital caps are mixed in the temporal, parietal and occipital lobes, it was difficult to distinguish an association with regional WMH. WMH increases with age, and is involved in the development of several geriatric conditions.[4] The cubed score of PVH using the modified Rotterdam scale might facilitate evaluation of WMH progression in daily clinical practice.

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Disclosure statement

The authors declare no conflict of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site: http://onlinelibrary.wiley.com/doi/10.1111/ggi.12664/suppinfo

Appendix S1 Details of the three visual rating scales.

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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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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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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

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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.

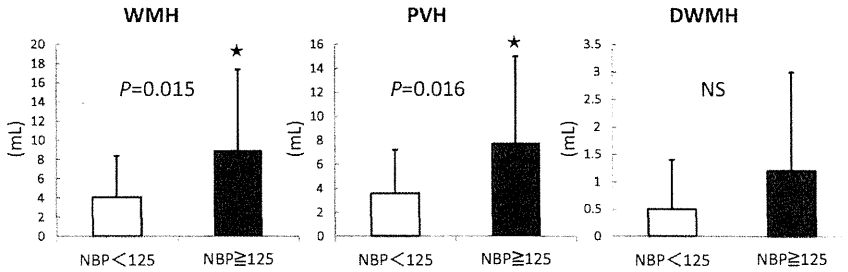

Figure 1 The relationship between night-time mean systolic blood pressure and white matter hyperintensity (WMH) volumes. WMH volume was significantly greater in the group with night-time systolic blood pressure (NBP) ≥125 mmHg than that in the <125 mmHg group, primarily attributed to elevated periventricular 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

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Disclosure statement

The authors declare no conflict of interest.

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REVIEW ARTICLE

White matter hyperintensities and geriatric syndrome: An important role of arterial stiffness

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White matter hyperintensities (WMH) are defined as cerebral white matter changes presumed to be of vascular origin, bilateral and mostly symmetrical. They can appear as hyperintense on T2-weighted and fluid-attenuated inversion recovery sequences, and as isointense or hypointense on T1-weighted magnetic resonance imaging of the brain. WMH have been focused on because of their clinical importance as a risk factor for cerebrovascular diseases and cognitive impairment. WMH are associated with geriatric syndrome, which is defined by clinical symptoms characteristic of older adults, including cognitive and functional impairment and falls.

Cerebral small vessel diseases, such as WMH, might play an important role as risk factors for cerebrovascular diseases, cognitive impairment and geriatric syndrome through the mechanism of arterial stiffness. However, the vascular, physiological and metabolic roles of arterial stiffness remain unclear. Basically, arterial stiffness indicates microvessel arteriosclerosis presenting with vascular endothelial dysfunction. These changes might arise from hemodynamic stress as a result of a "tsunami effect" on cerebral parenchyma. In the present article, we review the clinical characteristics of WMH, focusing particularly on two associations: (i) those between cerebral small vessel diseases including WMH and arterial stiffness; and (ii) those between WMH and geriatric syndrome. **Geriatr Gerontol Int 2015; 15 (Suppl. 1): 17–25.**

Keywords: arterial stiffness, cerebral small vessel disease, cognitive impairment, geriatric syndrome, white matter hyperintensities.

Introduction

White matter hyperintensities (WMH) are defined as cerebral white matter changes presumed to be of vascular origin, bilateral and mostly symmetrical. They can appear as hyperintense on T2-weighted and fluid-attenuated inversion recovery sequences, and as isointense or hypointense on T1-weighted magnetic resonance imaging of the brain (Fig. 1).[1] WMH have been focused on because of their clinical importance as a risk factor for cerebrovascular diseases and cognitive impairment. There are some variants of the term WMH, such as leukoaraiosis and white matter lesions (Table 1).[1] Generally, WMH are used in terminology regarding neuroimaging.

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Recently, the concept of vascular cognitive impairment (VCI) has become widespread, and the continuity of cerebrovascular diseases and cognitive impairment is one of the latest topics.[2] In particular, cerebral small vessel diseases (SVD) might play an important role as risk factors for both cerebrovascular diseases[3] and cognitive impairment.[4] This role could arise through the mechanism of arterial stiffness indicating microvessel arteriosclerosis presenting with vascular endothelial dysfunction (Fig. 2). Furthermore, recent studies suggest associations between arterial stiffness and geriatric syndrome.[5–8] Geriatric syndrome is relevant given an increasing aging society; geriatric syndrome is known to increase caregiver burden.[9,10] An increased number and proportion of older patients presenting with geriatric syndrome in populations of Japan and other countries contribute to the financial pressures on many healthcare systems. Herein, we review the characteristics of WMH, focusing particularly on two associations: those between cerebral SVD including WMH and arterial stiffness, and those between WMH and geriatric syndrome based on our previous studies.

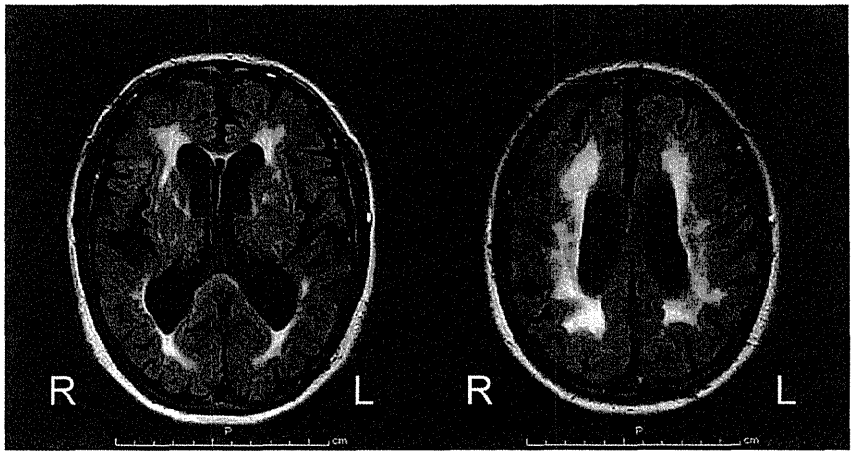

Figure 1 Brain magnetic resonance imaging of a representative patient presenting with white matter hyperintensities. Fluid-attenuated inversion recovery sequences of the brain magnetic resonance imaging show bilateral and symmetrical hyperintense on the periventricular white matter and subcortical lesions.

Table 1 Variants of the term: white matter hyperintensities[1]

Variants	(%)
Leukoaraiosis	31%
White matter lesions	24%
White matter hyperintensity	19%
White matter changes	12%
Leukoencephalopathy	7%
White matter disease	4%
White matter damage	0%
Ischemic white matter disease	0%

Data were derived from Reference 1: the use of this term in the title or abstract (n = 1144), using a structured literature search; for the methodology, search strategy and selection criteria, please see Reference 1.

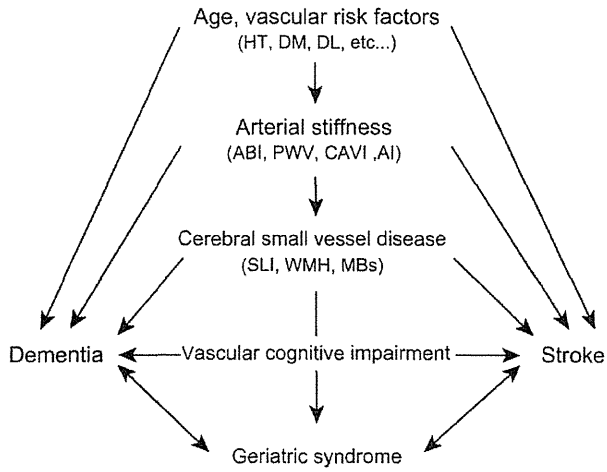

Figure 2 Schema of factors associated with geriatric syndrome. ABI, ankle-brachial index; AI, augmentation index; CAVI, cardio-ankle vascular index; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension; MB, cerebral microbleeds; PWV, pulse wave velocity; SLI, silent lacunar infarcts; WMH, white matter hyperintensities.

WMH and arterial stiffness

In general, arterial stiffness is a risk factor for mortality, cardiovascular diseases, cerebrovascular diseases and cognitive decline (Fig. 2).[3] There are some surrogate markers of arterial stiffness, such as the ankle-brachial index (ABI), pulse wave velocity (PWV; e.g. aortic, brachial-ankle and carotid-femoral PWV), cardio-ankle vascular index and the augmentation index. In this section, we review associations between WMH and cerebral damage, such as silent cerebral lesions, stroke, cognitive impairment and geriatric syndrome arising through the mechanism of arterial stiffness.

Silent cerebral lesions

Cerebral SVD, such as WMH, silent lacunar infarcts and cerebral microbleeds, have been considered as silent cerebral changes.[1,11] Furthermore, acute lacunar infarcts are associated with WMH, because the mechanism of acute lacunar infarcts mostly depends on cerebral SVD. In general, age and hypertension are well-known risk factors for cerebral SVD including WMH.[1] Similarly, calcifications in the carotid siphon might be a risk factor for cerebral SVD.[12]

Our studies show that arterial stiffness is independently associated with cerebral SVD, such as WMH and silent lacunar infarcts (Fig. 2).[13–15] The mechanism of cerebral SVD is considered to involve vascular endothelial dysfunction as a result of arterial stiffness, which causes blood–brain barrier failure or progression of arteriosclerotic changes and leads to cerebral parenchyma damage.[16] Taken together, there is a robust association between WMH and arterial stiffness, although there are some methodological differences among the surrogate markers of arterial stiffness.[15,17]

Stroke

Stroke is a major cause of long-term care requirements,[18] and lacunar infarcts are a common subtype of brain infarction in Japan.[19] Acute lacunar infarcts are associated with WMH.[19] There are sex differences regarding the risk factors and clinical outcomes in patients with acute lacunar infarcts.[19] Although hypertension and diabetes mellitus are common in both men and women, WMH are more prevalent in women. This difference might be as a result of an older age in women.

Acute lacunar infarcts sometimes induce progressive neurological deficits presenting with enlargement of infarcts. One of the risk factors for progressive neurological deficits is arterial stiffness.[16] This makes sense, because the mechanism of acute lacunar infarcts is based not only on traditional risk factors, such as hypertension and diabetes mellitus, but also cerebral SVD that is associated with arterial stiffness.[19] There are some clinical differences among the surrogate markers of arterial stiffness that have been assessed in patients with ischemic stroke.[17] Previously we suggested that: (i) a low ABI indicates advanced atherosclerosis; (ii) an increased brachial-ankle PWV strongly indicates cerebral SVD; and (iii) an increased cardio-ankle vascular index might indicate vessel stiffness as a result of arteriosclerosis.[17] WMH might be associated with any of these surrogate markers. Such clinical differences and associations should be clarified in detail in the future.

Cognitive impairment

WMH are a well-known risk factor for cognitive impairment.[20] Cognitive impairment including dementia is also independently associated with arterial stiffness.[21–24] An ABI greater than 1.30 and increased blood pressure variability are important predictors of cognitive impairment among patients without vascular diseases.[21] Furthermore, increased PWV is associated with cognitive impairment,[25] an independent predictor of cognitive decline,[23] and β-amyloid deposition in the brains of older adults.[4] These findings show that arterial stiffness is not only associated with arteriosclerosis, but also endothelial dysfunction or an unknown mechanism of the development of cognitive impairment, such as β-amyloid metabolism.

There are two vessel mechanisms related to cognitive impairment: cerebral amyloid angiopathy and cerebral SVD.[26,27] Cerebral microbleeds are associated with both cerebral amyloid angiopathy and cerebral SVD. Therefore, cerebral microbleeds are surrogate markers of both VCI and stroke. Recently, it was reported that chronic kidney disease is a risk factor for cognitive impairment[28] and acute lacunar infarcts.[29,30] This association is credible, because there are hemodynamic similarities between the vascular beds of the kidney and those of the brain.[30,31] Collectively, cognitive impairment might be affected by either cerebral amyloid angiopathy or cerebral SVD, both of which could be associated with arterial stiffness.

Table 2 Components associated with geriatric syndrome

Apathy
Balance disorder
Cognitive impairment
Dementia/delirium
Emotional incontinence
Falls/frailty/functional decline
Gait disturbance
Hard of hearing
Impaired appetite of unknown cause
Joint pain
Kinetic disorder
Lability
Motor weakness
Neuropsychiatric symptoms
Orientation disorder
Pressure ulcer
Quality-of-life impairment
Rachialgia
Sarcopenia/swallow disorder
Tremors
Urinary incontinence
Vision impairment
Weight loss

The abovementioned factors are frequently found in older adults; they might be caused by unknown/unexplained factors, and could lead to decreased activities of daily living.

Geriatric syndrome

Geriatric syndrome is defined by clinical symptoms that are characteristic of older adults, typically including cognitive and functional impairment, falls, aspiration of foreign bodies, impaired appetite of an unknown cause, frailty, and sarcopenia (Table 2).[32] The multidimensional and structured approach of a comprehensive geriatric assessment has been established to assess the presence of geriatric syndrome.[33]

Recently, associations between geriatric syndrome and arterial stiffness have been reported.[6–8] Frailty syndrome in older adults is associated with subclinical peripheral arterial disease indicated by ABI.[7] Increased brachial-ankle PWV is associated with increased risk of mortality and the onset of impairment in activities of daily living (ADL).[8] Higher aortic PWV is also associated with greater decline in psychomotor speed.[6] These factors could pose a risk for dementia; however, the direct association between geriatric syndrome and arterial stiffness is currently controversial, because geriatric syndrome includes various symptoms.

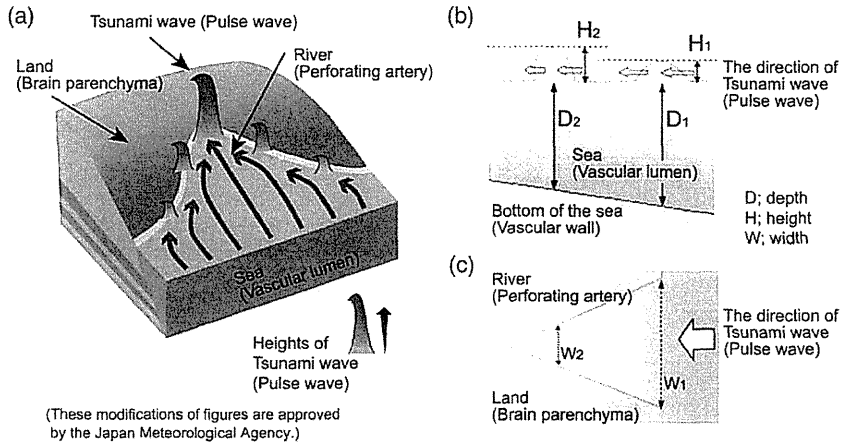

Figure 3 (a) An overview of the "tsunami wave model." The heights of the tsunami waves increase as the waves move closer to the land because of the geographical features of the bottom of the sea and/or river, and those of the seashore. This mechanism is as a result of (b) the depth of the bay and/or river, and (c) the width of the bay and/or river. Words given in parentheses are added by the authors to suggest that this tsunami wave model could explain the mechanism of the cerebral damages as shown by cerebral small vessel diseases, cognitive impairment, and geriatric syndrome as a result of increased pulse wave velocity. The details and data of the tsunami wave mechanism are available on the homepage of the Japan Meteorological Agency. (b) The vertical section. The heights of the tsunami waves increase ($H_1 \rightarrow H_2$) as the waves move closer to the land, because the depth of the sea and/or river ($D_1 \rightarrow D_2$) becomes shallower. (c) The horizontal section. The heights of the tsunami waves increase ($H_1 \rightarrow H_2$) as the waves move closer to the land, because the width of the sea and/or river ($W_1 \rightarrow W_2$) becomes narrower.

Mechanism

Numerous studies have reported associations between arterial stiffness and widespread cerebral damage in addition to other organ damage, such as the retina, heart and kidney. These organs have a common vascular mechanism consisting of perforating arteries. Therefore, we provide a hypothesis using the "tsunami wave model" for a better understanding of the risk and importance of arterial stiffness (Fig. 3). The images of the tsunami wave model show that wave damage toward a land area increases with the narrowing of a river (Fig. 3a). The mechanism of the tsunami waves is explained in terms of the increasing heights of tsunami waves as the waves move closer to the land; this is because of the geographical features of the bottom of the sea and/or the width of the river (Fig. 3b, 3c). The power of a tsunami wave depends on the degree of depths and widths of the bay and/or river. This tsunami wave model could explain the mechanism of cerebral damage as shown by cerebral SVD, cognitive impairment and geriatric syndrome as a result of increased PWV. Vascular narrowing due to atherosclerosis and vascular stiffness as a result of lipohyalinosis might accelerate the pulse waves. This issue will be investigated in more detail to clarify the mechanism.

WMH and geriatric syndrome

WMH are associated with various geriatric symptoms, such as falls, urinary incontinence, cognitive impairment, ADL and neuropsychiatric symptoms.[34–39] To date, numerous studies have shown that geriatric syndrome is associated with WMH. We have also shown associations between regional WMH and geriatric symptoms using the modified Rotterdam scale[35,37] and a semi-automatic program[36] in Japanese older adults with dementia. Next, we review our results together with previous reports for a link between regional WMH and various components of geriatric syndrome.

Motor performance

Gait and balance disorders are common causes of falls.[40] Some medications, such as tricyclic antidepressants, increase the risk of falls.[41] Early functional decline is also a risk factor for frailty.[42] Several studies have shown associations between WMH and motor disturbance, such as falls, balance disorders and gait disturbance.[35,43–52] Longitudinal and prospective studies show that both baseline WMH and progression of WMH predict gait disturbance, and increase the risk of falls.[44,47,49,53–55]

Differential roles of periventricular hyperintensities (PVH) and deep subcortical white matter hyperintensities (DWMH) in motor performance have been shown. Some studies show that both PVH and DWMH are associated with decreased motor performance,[35,51,56] whereas others show an association only with PVH.[44,53] The discrepancy in these findings might be as a result of differences among the study participants and/or the methodology of WMH measurement. Alternatively,

DeCarli *et al.* have shown that WMH extend smoothly from the ventricular wall as the overall WMH burden increases, suggesting no clear evidence for distinguishing WMH subtypes.[57]

Regarding regional WMH, WMH in the frontal lobes have critical effects on motor performance,[35,47,52] but WMH in occipital,[35] brain stem[51] and basal ganglia areas[58] are also suggested to have similar effects.

Considering the mechanisms of motor dysfunction as a result of WMH, WMH might interrupt neural networks and motor fibers. The frontal lobes are vulnerable regardless of the region of the WMH,[59] because the frontal cortex contains the frontal-subcortical circuits that link to the supplementary motor area, premotor cortex, motor cortex and somatosensory cortex.[60] Thus, WMH could interrupt the frontal-subcortical neural circuits and lead to motor balance disorders.

Urinary incontinence

Urinary incontinence is a troublesome symptom and decreases quality of life in older adults.[61] Several studies have shown associations between WMH and urinary incontinence.[36,50,62]

Incontinence increases with age.[63] The term "vascular incontinence" means incontinence as a result of disorders with a cerebral vascular component including WMH.[64,65] WMH are associated with urinary incontinence independent of brain atrophy,[36] and are more likely to be a strong risk factor compared with neurodegeneration as a result of Alzheimer's disease (AD).[66] Excess activity of the detrusor urinae muscle is a major cause of vascular incontinence, and patients with WMH might have hyperreflexia of the detrusor muscle.[67] Furthermore, increased urinary frequency is associated with severe WMH and leads to urinary incontinence.[67] These studies suggest that increased urinary frequency and urinary urgency are early clinical manifestations of WMH.

Regarding regional distribution of WMH in the brain, WMH in the frontal lobes is an independent risk factor for urinary incontinence in both older adults and demented adults.[36,68] In particular, WMH located in the right inferior frontal regions involve white matter tracts that belong to the anterior corona radiata and superior fronto-occipital fasciculus.[68] Urinary dysfunction is also associated with right frontal hypoperfusion in patients with idiopathic normal pressure hydrocephalus.[69] Thus, the frontal cortex is an important center of the micturition system,[68] and damage to the frontal lobes as a result of WMH may cause exaggerated micturition reflexes and dysfunction of the bladder system, leading to urinary incontinence.

Instrumental ADL

Instrumental ADL (IADL) require more complex and executive functions compared with basic ADL. Therefore, IADL might be easily impaired in the early stages of AD and sensitive to the progression of WMH. Previous studies show that WMH are associated with a decrease in IADL in non-disabled older adults,[70] in patients with mild cognitive impairment (MCI)[71,72] and dementia.[71–73] Furthermore, WMH severity is an independent risk factor for disability and death.[74]

Regarding regions of WMH, anterior PVH has an impact on frontal executive function and leads to a decrease in IADL.[72] Frontal executive dysfunction and cognitive performance might be affected mainly by PVH, but not by DWMH.[75] These results suggest that a decrease in IADL is more strongly associated with frontal lobe dysfunction, and is more closely associated with PVH compared with DWMH.

WMH severity associates with cognitive decline,[37,76] executive dysfunction,[70,77] motor disturbance[35,78] and depressive symptoms.[79,80] Because the frontal lobes have a convergence of fiber pathways and play an important role in these functions,[60] disruption in frontal tracts as a result of WMH easily lead to motor deterioration and cognitive decline that underlie impaired IADL performance.[81,82]

Behavioral and neuropsychiatric symptoms

Behavioral and psychological symptoms of dementia (BPSD) are neuropsychiatric symptoms and behaviors that frequently occur in patients with dementia. Previous studies show that WMH might worsen neuropsychiatric symptoms.[83–85] Specifically, WMH correlate with aberrant motor behavior,[62,84] anxiety[84] and night-time disturbance.[84] The BPSD might be a misconception of dementia.[86–88]

Both dementia and cerebrovascular diseases pose a strong risk for BPSD. Staekenborg *et al.* reported that BPSD was found in 92% of patients with vascular dementia (VaD), and apathy was most prevalent, followed by depression, irritability, and agitation and/or aggressiveness.[89] Large vessel-associated VaD is more related to agitation and aggression, whereas small vessel-associated VaD has more apathy, aberrant motor behavior and hallucinations.[89] Lacunar infarcts in the basal ganglia might increase the risk of delusions, hallucinations and depression.[85] In contrast, WMH are independently associated with the severity of BPSD in patients with AD.[83] Patients with AD who have a history of stroke have a three- to fourfold increased risk of BPSD.[90] These findings suggest the increased risk for developing BPSD in patients who have both dementia and cerebrovascular diseases.

In this connection, dementia subtypes, environmental factors as well as caregivers' factors, such as their attitude toward care recipients, might greatly influence the risk of BPSD in demented patients. For instance, outpatients with AD have more frequent night-time

behavior disturbances compared with those with VaD.[86] Patients with VaD living in nursing homes more frequently experience depression, irritability and appetite changes compared with those with AD.[86] These factors should be carefully taken into account for the analyses regarding the effects of WMH in future studies.

Cognitive impairment

The relationship between WMH and cognitive dysfunction has been reported in healthy older adults and in high-risk populations presenting with cognitive impairment. The Leukoaraiosis and Disability study investigated the clinical implication of WMH in non-disabled older adults, and showed that baseline WMH are highly correlated with global cognition, memory impairment, executive function, speed and motor control, attention, psychomotor speed, verbal fluency, naming, and visuoconstructional praxis.[91–93] Progression of WMH predicts a decrease in executive function, cognitive impairment and dementia.[94,95] Likewise, in high-risk populations for dementia, WMH are also associated with cognitive impairment. Defrancesco *et al.* reported that PVH and DWMH at baseline are negatively associated with psychomotor speed and visual memory, respectively, in MCI patients.[96]

WMH increase the risk of dementia in the older adults,[97] and predict conversion to dementia in MCI patients.[98,99] Roles of regional WMH have been shown. WMH volume in the parietal lobe specifically associates with AD.[100] Furthermore, PVH is significantly associated with an increased risk of progression from amnestic MCI to AD.[101] Both medial temporal lobe atrophy[98,99] and hippocampal volumes[102] with cerebral SVD are associated with conversion to AD or the other subtypes of dementia in MCI patients. Atrial fibrillation and diabetes could also be a risk factor for AD and VaD,[103,104] in addition to stroke.[105] These results support the notion that individuals with vascular pathologies have increased odds of dementia compared with individuals with a single pathology. In addition, the impact of cognitive reserve, such as premorbid intellectual function,[106] and the association of family functioning[107] and care assistive technology,[108] should be taken into account for preventing progression of cognitive decline.

Conclusion

WMH are well-known and important visual findings of brain magnetic resonance imaging in older adults with and without risk factors for cerebrovascular diseases and cognitive impairment. The vascular, physiological and metabolic roles of arterial stiffness as a risk factor for cerebral SVD including WMH have been discussed. Furthermore, various associations regarding WMH and geriatric syndromes have been elucidated. Improvement of living environment, management of risk factors, and innovation and development of novel drugs might suppress the progression of WMH, and reduce the risk of stroke and dementia.

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