Table 1 Comparison of neuropsychological tests between groups

Variables	Control ($n = 29$)	MCI EMCI ($n = 34$)	LMCI ($n = 37$)	F	P-value
Mini-Mental State Examination (score)	27.6 (2.0)	26.6 (1.9)	27.0 (1.9)	2.28	0.107
WMS-R Logical Memory II (score)	10.8 (2.4)	5.5 (1.6)†	1.2 (1.3)†‡	230.7	<0.0001
RCFT 3 min (score)	18.6 (5.6)	15.0 (6.0)†	14.0 (5.5)†	5.57	0.005
RCFT 30 min (score)	17.6 (5.5)	15.1 (5.8)	13.0 (6.5)†	4.81	0.01
DS forward (score)	8.3 (2.3)	7.8 (2.2)	7.4 (2.4)	1.28	0.283
DS backward (score)	5.9 (1.6)	5.4 (1.6)	4.6 (1.6)†	4.82	0.01
Letter fluency (numbers)	6.9 (3.1)	5.2 (2.0)†	5.3 (1.6)†	5.13	0.008
Category fluency (numbers)	16.6 (5.0)	15.8 (4.9)	12.9 (3.5)†‡	6.49	0.002

†Compared with normal for post-hoc analyses at $P < 0.05$. ‡Compared between EMCI and LMCI for post-hoc analyses at $P < 0.05$. Values are means (SD) or proportion. Group differences were tested in all data using ANOVA. The statistical data are presented as F and P-value. Control, control subjects without objective memory impairments; DS, digit span; EMCI, the early stage in amnesic mild cognitive impairment; LMCI, the late stage in amnesic mild cognitive impairment; MCI, mild cognitive impairment; RCFT, Rey–Osterrieth complex figure test; WMS-R, Wechsler Memory Scale-Revised.

ability and executive function.[25,27,28] We carried out a digit span forward test (DSF) and a digit span backward test (DSB). Both tests are subsets of the Wechsler Adult Intelligence Scale III, and require participants to repeat a series of verbally-presented digits of increasing length in forward and backward order.[25] Performance on the digit span task strongly depends on working memory, cognitive regulation and manipulation, all of which are components of executive function.

Statistical analyses

Analyses of variance (ANOVA) or χ^2-tests (for sex) were carried out to determine the differences in demographic data between the control, EMCI and LMCI groups. The comparison of each neuropsychological test between groups was analyzed using ANOVA and Tukey–Kramer honestly significant difference post-hoc tests. In addition, logistic regression analysis was carried out to identify the relationship between neuropsychological tests and cognitive impairment status. Crude odds ratios were calculated for each test (model 1) and logistic regression analysis was carried out, adjusted for age and sex (model 2). To examine the association between verbal memory and other neuropsychological tests, Pearson's correlation coefficients were calculated. We also used linear regression to assess the relationships between neuropsychological variables while controlling for age and sex. Statistical significance was set at $P < 0.05$. All analyses were carried out using commercially available software (JMP8.0J, SAS Institute Japan, Tokyo, Japan) for Windows.

Results

Demographic characteristics (control: age = 72.8 ± 4.7, proportion of women = 62%, educational history = 10.3 ± 2.3; EMCI: age = 75.4 ± 7.2, proportion of women = 56%, educational history = 10.4 ± 2.1; LMCI: age = 76.8 ± 7.5, proportion of women = 41%, educational history = 11.3 ± 2.9) were not different between groups (age: $F = 2.62$, $P = 0.08$; sex: $\chi^2 = 3.35$, $P = 0.19$; educational history: $F = 1.69$, $P = 0.19$). The results of the neuropsychological measures are presented in Table 1. MMSE scores did not differ between groups. Group effects were observed in the RCFT (3 min: $P < 0.01$, 30 min: $P = 0.01$), DSB ($P = 0.01$), letter fluency ($P < 0.01$) and category fluency ($P < 0.01$). Both EMCI and LMCI showed lower function of letter fluency ($P = 0.01$) and WMS than the control ($P < 0.01$). DSB significantly decreased in LMCI compared with the control ($P = 0.01$), but not between other groups. DSF was not significantly different between groups. Scores in the neuropsychological tests, other than category fluency ($P = 0.02$) and logical memory ($P < 0.01$), did not differ between EMCI and LMCI. Table 2 shows the results of logistic regression analysis of the neuropsychological test results, discriminating EMCI subjects from control or LMCI subjects. In the control and EMCI groups, the RCF 3 min (model 1: $P = 0.02$, model 2: $P = 0.04$) and letter fluency (model 1: $P = 0.03$, model 2: $P = 0.04$) showed significant associations, whereas only category fluency (model 1: $P < 0.01$, model 2: $P < 0.01$) showed a significant difference between the EMCI and LMCI groups.

Table 3 shows the relationships of WMS-R Logical Memory II test with the neuropsychological tests. Over all participants, the WMS-R Logical Memory II test was significantly associated with RCFT 3 min, RCFT 30 min, DSB, letter fluency and category fluency scores, even after controlling for age and sex. In the EMCI group, DSB, letter fluency and category fluency were significantly related to WMS-R Logical Memory II test scores. However, there were no significant relationships

Table 2 The results of logistic regression in neuropsychological tests for discriminating early stage in amnesic mild cognitive impairment subjects from control or late stage in amnesic mild cognitive impairment subjects

Variables	Control and EMCI ($n = 63$) Odds ratio (95% CI)		EMCI and LMCI ($n = 71$) Odds ratio (95% CI)	
	Model 1	Model 2	Model 1	Model 2
RCFT 3 min	0.90 (0.82–0.99)*	0.91 (0.83–0.99)*	0.97 (0.89–1.05)	0.97 (0.89–1.06)
RCFT 30 min	0.92 (0.84–1.01)	0.94 (0.85–1.03)	0.94 (0.87–1.02)	0.94 (0.87–1.02)
DS forward	0.89 (0.71–1.12)	0.89 (0.70–1.12)	0.93 (0.76–1.15)	0.92 (0.74–1.15)
DS backward	0.82 (0.60–1.14)	0.87 (0.62–1.22)	0.75 (0.55–1.02)	0.74 (0.54–1.03)
Letter fluency	0.91 (0.83–0.99)*	0.91 (0.83–0.99)*	1.00 (0.92–1.09)	0.99 (0.91–1.09)
Category fluency	0.97 (0.88–1.07)	0.99 (0.89–1.10)	0.84 (0.74–0.96)**	0.82 (0.71–0.94)**

*$P < 0.05$; **$P < 0.01$. Model 1 is a crude model and model 2 was conducted adjusting for age and sex. CI, confidential interval; Control, control subjects without objective memory impairments; DS, digit span; EMCI, the early stage in amnesic mild cognitive impairment; LMCI, the late stage in amnesic mild cognitive impairment; RCFT, Rey–Osterrieth complex figure test.

Table 3 Relationships between the Wechsler Memory Scale-Revised Logical Memory II test and neuropsychological tests

Variables	Total		EMCI		LMCI	
	r	β	*r*	β	*r*	β
RCF 3 min	0.36**	0.30**	0.04	−0.0002	0.11	0.21
RCF 30 min	0.33**	0.26**	0.05	−0.01	0.03	0.10
DS forward	0.13	0.08	0.28	0.16	−0.09	−0.07
DS backward	0.35**	0.29**	0.64**	0.59**	−0.20	−0.18
Letter fluency	0.32**	0.28**	0.48**	0.39*	−0.19	−0.22
Category fluency	0.39**	0.35**	0.43*	0.35*	0.20	0.16

*$P < 0.05$; **$P < 0.01$. Pearson *r*-values represent the simple correlation between the Wechsler Memory Scale-Revised Logical Memory II test and the dependent variables. A standardized beta (β) represents the correlation between logical memory and each dependent variable after controlling for age and sex. Control, control subjects without objective memory impairments; DS, digit span; EMCI, the early stage in amnesic mild cognitive impairment; LMCI, the late stage in amnesic mild cognitive impairment; RCFT, Rey–Osterrieth complex figure test.

between the WMS-R Logical Memory II test and the other neuropsychological measurements in the LMCI group.

Discussion

The present preliminary study shows the characteristics of cognitive function in EMCI and LMCI participants. We classified the participants into three groups by the stage of aMCI, showing group differences in cognitive decline. Significantly lower neuropsychological performance scores in RCFT, DSB, letter fluency and category fluency were found in the LMCI group compared with control participants. The EMCI group also showed significantly lower cognitive performance in the letter fluency and RCFT compared with the control group, whereas significant differences in cognitive function between the EMCI and LMCI groups were only found in the category fluency and in the WMS-R Logical Memory II test. These group differences remained after adjusting for age and sex. These findings suggest that this method is useful in distinguishing EMCI from other groups. The correlational analysis further examined the characteristics of EMCI. A significant relationship between WMS-R Logical Memory II test with verbal fluency and DSB was confirmed in the EMCI participants, but not LMCI participants, after adjusting for age and sex.

Decline in cognitive function was mainly observed in memory, and other cognitive functions also deteriorated in elderly participants with MCI. The present results in LMCI participants are consistent with other studies in which aMCI subjects showed lower performance in the RCFT,[29] DSB[30] and verbal fluency test[30–33] compared with control subjects. The decline of RCFT and letter fluency performance also occurred in EMCI individuals in the present study. RCFT performance reflects the

visual memory involved in both encoding and retrieval tasks, and EMCI individuals showed lower performance than the control group in the 3-min task, but not in the 30-min task. This discrepancy in RCFT was likely a result of task difficulty. The degree of task difficulty for cognitive dysfunction subjects (e.g. MCI or AD patients) affects neuropsychological performance, and overly difficult tasks are not useful for assessing these disorders.[34] Digit span performance also differed between tasks in the current study. The DSF and DSB tests evaluate executive function, including attention, and the DSB further requires working memory.[25] These differences might have played a role in the differing results between the two digit span tests.

Verbal fluency assessed the ability to express language and executive function.[25,27,28] The present results were also consistent with the decline of both letter and category fluency, which were observed in LMCI.[32] In addition, the decline of letter fluency occurred in EMCI individuals, whereas category fluency did not differ between control and EMCI subjects, but was different between EMCI and LMCI subjects. These letter fluency and category fluency results show a discrepancy in verbal fluency ability. This discrepancy might be based on the differences of the neuronal requirements of these tasks. Letter fluency is thought to rely on a neural network involving the left prefrontal and inferior parietal cortex, whereas category fluency involves the frontal and temporal regions.[35] Although it is unclear which tasks of letter fluency and category fluency are most useful for detection of MCI, the present results indicate that both letter fluency and category fluency might depend on the severity of memory impairment in aMCI. Although category fluency is generally more frequently impaired in AD, worse letter fluency has also been reported.[35] The present results indicate that impairments of letter fluency may be a characteristic of EMCI. However, the sample size or study design of the present study might have limited the generalizability of these findings. The etiological data confirmed that the decline of cognitive function in aMCI, but not memory, was also a risk for conversion to AD.[10–12] The present results indicate that screening for EMCI should not only involve a verbal memory test, but also measurements of other domains.

The correlation analysis shows characteristics of cognitive function in EMCI. A variety of executive functions, including verbal fluency and DSB performance, were associated with logical memory in the EMCI group. However, there was no significant relationship in the LMCI group. These results remained after controlling for age and sex. Many neuroimaging studies have shown that memory impairment in aMCI and AD is induced by structural and functional changes in the MTL region.[6,8,9] Activation in the MTL region during MCI transforms from hyperactivation to hypoactivation according to the severity of cognitive function during the progression of MCI to AD, and hyperactivation in the MTL confirms a functional compensatory mechanism in very early MCI.[5,6] This compensation might occur as a result of an abnormal functional connectivity or network within the brain.[13–16] Activation of the MTL alone is not sufficient for successful memory function, and the MTL region shows strong connectivity with the cingulate cortex and frontal lobe within the memory network, which is decreased in aMCI and AD.[13,17,36] DSB performance has been found to activate the frontal lobe,[37] whereas verbal fluency tests activate in the prefrontal lobe, parietal lobe, frontal lobe and temporal lobe.[38,39] Additionally, the frontal lobe is a key region involved in human memory processing. Large corticocortical direct reciprocal connections exist between the frontal lobe and the MTL.[40] The characteristic relationship between logical memory and a part of executive function in EMCI patients might be caused by a functional abnormality in the brain network. Further studies should be carried out to confirm this hypothesis, using neuroimaging methods, such as functional magnetic resonance imaging.

Several limitations of the current study must be considered. First, the sample size was relatively small, introducing potential difficulties in avoiding heterogeneity in the MCI subjects. Second, the study was cross-sectional. The association between memory function and other cognitive domains should be investigated in prospective and neuroimaging studies. MCI is a reversible state in the spectrum of normal aging-MCI-AD. Clarifying the characteristics of cognitive function in EMCI during conversion to AD is important, and requires a longitudinal study. Finally, the present study did not include data involving apolipoprotein E ε4, amyloid status and cerebrospinal fluid biomarkers. These limitations should be taken into consideration when interpreting the current findings.

In conclusion, elderly adults with MCI showed deterioration not only in memory, but also in executive function, and the memory decline corresponded with poorer performance in executive function. The present preliminary results show that comprehensive assessments that include memory and executive functions might be required to distinguish elderly adults with MCI from cognitively normal elderly adults. Future research is required to determine appropriate neuropsychological tests for predicting the conversion of EMCI and LMCI to AD.

Acknowledgments

This work was supported by a grant from the Japanese Ministry of Health, Labour and Welfare (project for optimizing long-term care; B-3 to T. S.). We thank the Obu city office for the help provided in

participant recruitment, and the speech therapists of the Ukai rehabilitation hospital for assistance with data collection.

Disclosure statement

The authors have no financial or any other kinds of conflicts with this paper.

References

1 Petersen RC, Doody R, Kurz A *et al.* Current concepts in mild cognitive impairment. *Arch Neurol* 2001; **58**: 1985–1992.
2 Winblad B, Palmer K, Kivipelto M *et al.* Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004; **256**: 240–246.
3 Gauthier S, Reisberg B, Zaudig M *et al.* Mild cognitive impairment. *Lancet* 2006; **367**: 1262–1270.
4 Petersen RC, Roberts RO, Knopman DS *et al.* Mild cognitive impairment: ten years later. *Arch Neurol* 2009; **66**: 1447–1455.
5 Dickerson BC, Sperling RA. Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging. *Behav Neurol* 2009; **21**: 63–75.
6 Pihlajamaki M, Jauhiainen AM, Soininen H. Structural and functional MRI in mild cognitive impairment. *Curr Alzheimer Res* 2009; **6**: 179–185.
7 Weiner MW, Aisen PS, Jack CR Jr *et al.* The Alzheimer's disease neuroimaging initiative: progress report and future plans. *Alzheimers Dement* 2010; **6**: 202 e7–211 e7.
8 Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004; **256**: 183–194.
9 Wolf H, Jelic V, Gertz HJ, Nordberg A, Julin P, Wahlund LO. A critical discussion of the role of neuroimaging in mild cognitive impairment. *Acta Neurol Scand Suppl* 2003; **179**: 52–76.
10 Blacker D, Lee H, Muzikansky A *et al.* Neuropsychological measures in normal individuals that predict subsequent cognitive decline. *Arch Neurol* 2007; **64**: 862–871.
11 Rozzini L, Chilovi BV, Conti M *et al.* Conversion of amnestic Mild Cognitive Impairment to dementia of Alzheimer type is independent to memory deterioration. *Int J Geriatr Psychiatry* 2007; **22**: 1217–1222.
12 Tabert MH, Manly JJ, Liu X *et al.* Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Arch Gen Psychiatry* 2006; **63**: 916–924.
13 Bai F, Zhang Z, Watson DR *et al.* Abnormal functional connectivity of hippocampus during episodic memory retrieval processing network in amnestic mild cognitive impairment. *Biol Psychiatry* 2009; **65**: 951–958.
14 Davidson PS, Troyer AK, Moscovitch M. Frontal lobe contributions to recognition and recall: linking basic research with clinical evaluation and remediation. *J Int Neuropsychol Soc* 2006; **12**: 210–223.
15 Trivedi MA, Murphy CM, Goetz C *et al.* fMRI activation changes during successful episodic memory encoding and recognition in amnestic mild cognitive impairment relative to cognitively healthy older adults. *Dement Geriatr Cogn Disord* 2008; **26**: 123–137.
16 Fouquet M, Desgranges B, Landeau B *et al.* Longitudinal brain metabolic changes from amnestic mild cognitive impairment to Alzheimer's disease. *Brain* 2009; **132**: 2058–2067.
17 Bai F, Liao W, Watson DR *et al.* Abnormal whole-brain functional connection in amnestic mild cognitive impairment patients. *Behav Brain Res* 2011; **216**: 666–672.
18 Chang YL, Jacobson MW, Fennema-Notestine C *et al.* Level of executive function influences verbal memory in amnestic mild cognitive impairment and predicts prefrontal and posterior cingulate thickness. *Cereb Cortex* 2010; **20**: 1305–1313.
19 Chen TF, Chen YF, Cheng TW, Hua MS, Liu HM, Chiu MJ. Executive dysfunction and periventricular diffusion tensor changes in amnesic mild cognitive impairment and early Alzheimer's disease. *Hum Brain Mapp* 2009; **30**: 3826–3836.
20 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.
21 Yesavage JA. Geriatric depression scale. *Psychopharmacol Bull* 1988; **24**: 709–711.
22 Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol* 2005; **62**: 1160–1163; discussion 67.
23 Wechsler D. *Wechsler Memory Scale-Revised Manual.* San Antonio, TX: The Psychological Corporation, 1987.
24 Alzheimer's Disease Neuroimaging Initiative. Alzheimer's Disease Neuroimaging Initiative Grand Opportunity. 2010. [Cited 1 Aug 2011.] Available from URL: http://www.adni-info.org/Scientists/AboutADNI.aspx
25 Lezak MD. *Neuropsychological Assessment,* 4th edn. New York: Oxford University Press, 2004.
26 Meyers JE, Meyers KR. *Rey Complex Figure Test and Recognition Trial.* Odessa, TX: Psychological Assessment Resources, 1995.
27 Benton AL. Differential behavioral effects in frontal lobe disease. *Neuropsychologia* 1968; **6**: 53–60.
28 Nemoto T, Kashima H, Mizuno M. Contribution of divergent thinking to community functioning in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31**: 517–524.
29 Kasai M, Meguro K, Hashimoto R, Ishizaki J, Yamadori A, Mori E. Non-verbal learning is impaired in very mild Alzheimer's disease (CDR 0.5): normative data from the learning version of the Rey-Osterrieth Complex Figure Test. *Psychiatry Clin Neurosci* 2006; **60**: 139–146.
30 Muangpaisan W, Intalapaporn S, Assantachai P. Digit span and verbal fluency tests in patients with mild cognitive impairment and normal subjects in Thai-community. *J Med Assoc Thai* 2010; **93**: 224–230.
31 Murphy KJ, Rich JB, Troyer AK. Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer's type dementia. *J Int Neuropsychol Soc* 2006; **12**: 570–574.
32 Nutter-Upham KE, Saykin AJ, Rabin LA *et al.* Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. *Arch Clin Neuropsychol* 2008; **23**: 229–241.
33 Duff K, Hobson VL, Beglinger LJ, O'Bryant SE. Diagnostic accuracy of the RBANS in mild cognitive impairment: limitations on assessing milder impairments. *Arch Clin Neuropsychol* 2010; **25**: 429–441.
34 Small GW, Bookheimer SY, Thompson PM *et al.* Current and future uses of neuroimaging for cognitively impaired patients. *Lancet Neurol* 2008; 7: 161–172.

35 Laws KR, Duncan A, Gale TM. "Normal" semantic-phonemic fluency discrepancy in Alzheimer's disease? A meta-analytic study. *Cortex* 2010; **46**: 595–601.
36 Choo IH, Lee DY, Oh JS *et al.* Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 2010; **31**: 772–779.
37 Owen AM. The role of the lateral frontal cortex in mnemonic processing: the contribution of functional neuroimaging. *Exp Brain Res* 2000; **133**: 33–43.
38 Hirono N, Mori E, Ishii K *et al.* Neuronal substrates for semantic memory: a positron emission tomography study in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2001; **12**: 15–21.
39 Pihlajamaki M, Tanila H, Hanninen T *et al.* Verbal fluency activates the left medial temporal lobe: a functional magnetic resonance imaging study. *Ann Neurol* 2000; **47**: 470–476.
40 Rempel-Clower NL, Barbas H. The laminar pattern of connections between prefrontal and anterior temporal cortices in the Rhesus monkey is related to cortical structure and function. *Cereb Cortex* 2000; **10**: 851–865.

Geriatr Gerontol Int 2015; **15 (Suppl. 1):** *17–25*

REVIEW ARTICLE

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

Naoki Saji,[1] Noriko Ogama,[1,2,3] Kenji Toba[1] and Takashi Sakurai[1]

[1]*Center for Comprehensive Care and Research on Memory Disorders,* [2]*Biobank, National Center for Geriatrics and Gerontology, Obu, and* [3]*Department of Community Healthcare and Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan*

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.

Accepted for publication 2 October 2015.

Correspondence: Dr Naoki Saji MD PhD, Center for Comprehensive Care and Research on Memory Disorders, National Center for Geriatrics and Gerontology, 7-430, Morioka, Obu, Aichi 474-8511, Japan. Email: sajink@nifty.com

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.

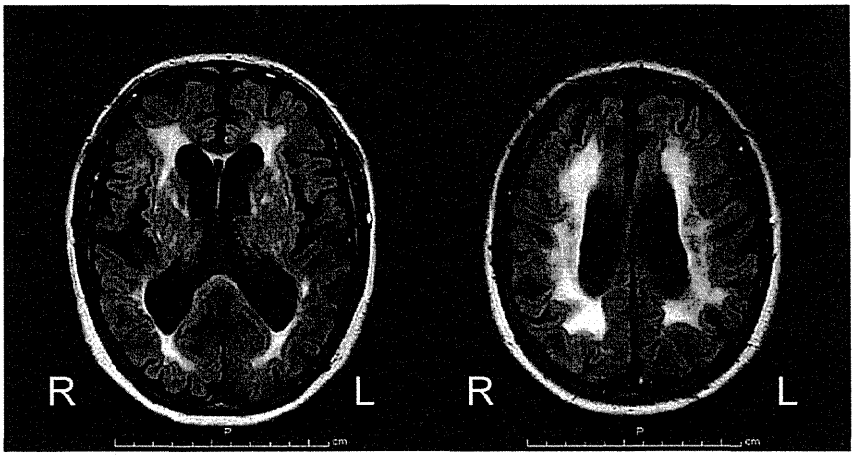

Figure 1 Brain magnetic resonance imaging of a representative patient presenting with white matter hyperintensities. Fluid-attenuated inversion recovery sequences of the brain magnetic resonance imaging show bilateral and symmetrical hyperintense on the periventricular white matter and subcortical lesions.

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.

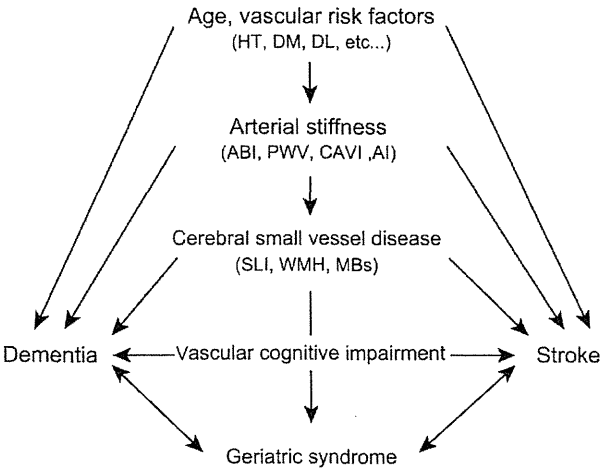

Figure 2 Schema of factors associated with geriatric syndrome. ABI, ankle-brachial index; AI, augmentation index; CAVI, cardio-ankle vascular index; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension; MB, cerebral microbleeds; PWV, pulse wave velocity; SLI, silent lacunar infarcts; WMH, white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

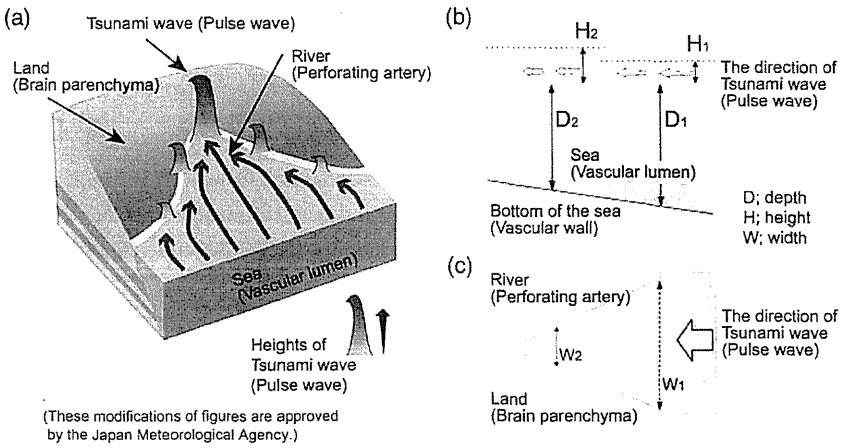

Figure 3 (a) An overview of the "tsunami wave model." The heights of the tsunami waves increase as the waves move closer to the land because of the geographical features of the bottom of the sea and/or river, and those of the seashore. This mechanism is as a result of (b) the depth of the bay and/or 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.

Acknowledgments

We are grateful to Kyoko Banno and Natsuyo Kimoto for their secretarial assistance. Dr Naoki Saji contributed to manuscript drafting/revision, study design, data analysis and interpretation, data acquisition, and study supervision. Ms Noriko Ogama contributed to manuscript drafting/revision, study design, data analysis and interpretation, and data acquisition. Professor Kenji Toba contributed to study supervision. Dr Takashi Sakurai contributed to manuscript revision, study design, data analysis and interpretation, and study supervision.

Disclosure statement

This work was financially supported by grants from Research Funding of Longevity Sciences (25-6) from the National Center for Geriatrics and Gerontology (NCGG) and by a research grant, Grants-in-Aid for Scientific Research (No. 26870765), from the Japan Society for the Promotion of Science.

References

1 Wardlaw JM, Smith EE, Biessels GJ *et al.* Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; **12**: 822–838.
2 Gorelick PB, Scuteri A, Black SE *et al.* Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; **42**: 2672–2713.
3 Kim J, Song TJ, Song D *et al.* Brachial-ankle pulse wave velocity is a strong predictor for mortality in patients with acute stroke. *Hypertension* 2014; **64**: 240–246.
4 Hughes TM, Kuller LH, Barinas-Mitchell EJ *et al.* Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults. *Neurology* 2013; **81**: 1711–1718.
5 Zhong W, Cruickshanks KJ, Schubert CR *et al.* Pulse wave velocity and cognitive function in older adults. *Alzheimer Dis Assoc Disord* 2014; **28**: 44–49.
6 Watson NL, Sutton-Tyrrell K, Rosano C *et al.* Arterial stiffness and cognitive decline in well-functioning older adults. *J Gerontol A Biol Sci Med Sci* 2011; **66**: 1336–1342.
7 Lin CH, Chou CY, Liu CS, Huang CY, Li TC, Lin CC. Association between frailty and subclinical peripheral vascular disease in a community-dwelling geriatric population: taichung community Health Study for Elders. *Geriatr Gerontol Int* 2015; **15**: 261–267.

8 Kuroiwa Y, Miyano I, Nishinaga M *et al.* Association between level of brachial-ankle pulse wave velocity and onset of activities of daily living impairment in community-dwelling older individuals. *Geriatr Gerontol Int* 2015; **15**: 840–847.
9 Kamiya M, Sakurai T, Ogama N, Maki Y, Toba K. Factors associated with increased caregivers' burden in several cognitive stages of Alzheimer's disease. *Geriatr Gerontol Int* 2014; **14** (Suppl 2): 45–55.
10 Sakurai H, Hanyu H, Terayama H *et al.* Factors associated with the burden of caregivers of patients with dementia. *Geriatr Gerontol Int* 2015; **15**: 384–385.
11 Yates PA, Villemagne VL, Ellis KA, Desmond PM, Masters CL, Rowe CC. Cerebral microbleeds: a review of clinical, genetic, and neuroimaging associations. *Front Neurol* 2014; **4**: 205.
12 Del Brutto OH, Mera RM, Gillman J, Ha J, Zambrano M. Calcifications in the carotid siphon correlate with silent cerebral small vessel disease in community-dwelling older adults: a population-based study in rural ecuador. *Geriatr Gerontol Int* 2015 (Sep 3); doi: 10.1111/ggi.12599; [Epub ahead of print].
13 Saji N, Shimizu H, Kawarai T, Tadano M, Kita Y, Yokono K. Increased brachial-ankle pulse wave velocity is independently associated with white matter hyperintensities. *Neuroepidemiology* 2011; **36**: 252–257.
14 Saji N, Kimura K, Shimizu H, Kita Y. Association between silent brain infarct and arterial stiffness indicated by brachial-ankle pulse wave velocity. *Intern Med* 2012; **51**: 1003–1008.
15 Saji N, Kimura K, Shimizu H, Kita Y. Silent brain infarct is independently associated with arterial stiffness indicated by cardio-ankle vascular index (CAVI). *Hypertens Res* 2012; **35**: 756–760.
16 Saji N, Kimura K, Kawarai T, Shimizu H, Kita Y. Arterial stiffness and progressive neurological deficit in patients with acute deep subcortical infarction. *Stroke* 2012; **43**: 3088–3090.
17 Saji N, Kimura K, Yagita Y, Kawarai T, Shimizu H, Kita Y. Comparison of arteriosclerotic indicators in patients with ischemic stroke: ankle-brachial index, brachial-ankle pulse wave velocity, and cardio-ankle vascular index. *Hypertens Res* 2015; **38**: 323–328.
18 Saji N, Kimura K, Ohsaka G *et al.* Functional independence measure scores predict level of long-term care required by patients after stroke: a multicenter retrospective cohort study. *Disabil Rehabil* 2015; **37**: 331–337.
19 Saji N, Shimizu H, Kawarai T, Tadano M, Kita Y, Yokono K. Clinical features of a first-ever lacunar infarction in Japanese patients: poor outcome in females. *J Stroke Cerebrovasc Dis* 2011; **20**: 231–235.
20 Makino T, Umegaki H, Suzuki Y *et al.* Relationship between small cerebral white matter lesions and cognitive function in patients with Alzheimer's disease and amnestic mild cognitive impairment. *Geriatr Gerontol Int* 2014; **14**: 819–826.
21 Gutierrez J, Marshall RS, Lazar RM. Indirect measures of arterial stiffness and cognitive performance in individuals without traditional vascular risk factors or disease. *JAMA Neurol* 2015; **72**: 309–315.
22 Hughes TM, Craft S, Lopez OL. Review of 'the potential role of arterial stiffness in the pathogenesis of Alzheimer's disease'. *Neurodegener Dis Manag* 2015; **5**: 121–135.
23 Taniguchi Y, Fujiwara Y, Nofuji Y *et al.* Prospective study of arterial stiffness and subsequent cognitive decline among community-dwelling older Japanese. *J Epidemiol* 2015; **25**: 592–599.
24 Yukutake T, Yamada M, Fukutani N *et al.* Arterial stiffness predicts cognitive decline in Japanese community-dwelling elderly subjects: a one-year follow-up study. *J Atheroscler Thromb* 2015; **22**: 637–644.
25 Scuteri A, Wang H. Pulse wave velocity as a marker of cognitive impairment in the elderly. *J Alzheimers Dis* 2014; **42** (Suppl 4): S401–S410.
26 Tomimoto H. Subcortical vascular dementia. *Neurosci Res* 2011; **71**: 193–199.
27 Gustavsson AM, Stomrud E, Abul-Kasim K *et al.* Cerebral microbleeds and white matter hyperintensities in cognitively healthy elderly: a cross-sectional cohort study evaluating the effect of arterial stiffness. *Cerebrovasc Dis Extra* 2015; **5**: 41–51.
28 Miwa K, Tanaka M, Okazaki S *et al.* Chronic kidney disease is associated with dementia independent of cerebral small-vessel disease. *Neurology* 2014; **82**: 1051–1057.
29 Saji N, Kimura K, Yagita Y *et al.* Deep cerebral microbleeds and renal dysfunction in patients with acute lacunar infarcts. *J Stroke Cerebrovasc Dis* 2015 Aug 28. pii: S1052-3057(15)00396-1. doi: 10.1016/j.jstrokecerebrovasdis.2015.07.010. [Epub ahead of print]
30 Saji N, Sato T, Sakuta K *et al.* Chronic kidney disease is an independent predictor of adverse clinical outcomes in patients with recent small subcortical infarcts. *Cerebrovasc Dis Extra* 2014; **4**: 174–181.
31 Cho AH, Lee SB, Han SJ, Shon YM, Yang DW, Kim BS. Impaired kidney function and cerebral microbleeds in patients with acute ischemic stroke. *Neurology* 2009; **73**: 1645–1648.
32 Arai H, Ouchi Y, Toba K *et al.* Japan as the front-runner of super-aged societies: perspectives from medicine and medical care in Japan. *Geriatr Gerontol Int* 2015; **15**: 673–687.
33 Namioka N, Hanyu H, Hatanaka H, Fukasawa R, Sakurai H, Iwamoto T. Comprehensive geriatric assessment in elderly patients with dementia. *Geriatr Gerontol Int* 2015; **15**: 27–33.
34 Kuo HK, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol A Biol Sci Med Sci* 2004; **59**: 818–826.
35 Ogama N, Sakurai T, Shimizu A, Toba K. Regional white matter lesions predict falls in patients with amnestic mild cognitive impairment and Alzheimer's disease. *J Am Med Dir Assoc* 2014; **15**: 36–41.
36 Ogama N, Yoshida M, Nakai T, Niida S, Toba K, Sakurai T. Frontal white matter hyperintensity predicts lower urinary tract dysfunction in older adults with amnestic mild cognitive impairment and Alzheimer's disease. *Geriatr Gerontol Int* 2015 (Jan 22); doi: 10.1111/ggi.12447; [Epub ahead of print].
37 Akisaki T, Sakurai T, Takata T *et al.* Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT). *Diabetes Metab Res Rev* 2006; **22**: 376–384.
38 Mortamais M, Artero S, Ritchie K. White matter hyperintensities as early and independent predictors of Alzheimer's disease risk. *J Alzheimers Dis* 2014; **42** (Suppl 4): S393–S400.
39 Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2010; **341**: c3666.
40 Doi T, Shimada H, Park H *et al.* Cognitive function and falling among older adults with mild cognitive

impairment and slow gait. *Geriatr Gerontol Int* 2014; **15**: 1073–1078.
41 Chiu MH, Lee HD, Hwang HF, Wang SC, Lin MR. Medication use and fall-risk assessment for falls in an acute care hospital. *Geriatr Gerontol Int* 2015; **15**: 856–863.
42 Beaton K, McEvoy C, Grimmer K. Identifying indicators of early functional decline in community-dwelling older people: a review. *Geriatr Gerontol Int* 2015; **15**: 133–140.
43 Murray ME, Senjem ML, Petersen RC *et al.* Functional impact of white matter hyperintensities in cognitively normal elderly subjects. *Arch Neurol* 2010; **67**: 1379–1385.
44 Soumaré A, Elbaz A, Zhu Y *et al.* White matter lesions volume and motor performances in the elderly. *Ann Neurol* 2009; **65**: 706–715.
45 Moscufo N, Guttmann CR, Meier D *et al.* Brain regional lesion burden and impaired mobility in the elderly. *Neurobiol Aging* 2011; **32**: 646–654.
46 Srikanth V, Beare R, Blizzard L *et al.* Cerebral white matter lesions, gait, and the risk of incident falls: a prospective population-based study. *Stroke* 2009; **40**: 175–180.
47 Srikanth V, Phan TG, Chen J, Beare R, Stapleton JM, Reutens DC. The location of white matter lesions and gait–a voxel-based study. *Ann Neurol* 2010; **67**: 265–269.
48 Rosano C, Brach J, Longstreth Jr WT, Newman AB. Quantitative measures of gait characteristics indicate prevalence of underlying subclinical structural brain abnormalities in high-functioning older adults. *Neuroepidemiology* 2006; **26** (1): 52–60.
49 Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc* 2005; **53**: 649–654.
50 Sonohara K, Kozaki K, Akishita M *et al.* White matter lesions as a feature of cognitive impairment, low vitality and other symptoms of geriatric syndrome in the elderly. *Geriatr Gerontol Int* 2008; **8**: 93–100.
51 Starr JM, Leaper SA, Murray AD *et al.* Brain white matter lesions detected by magnetic resonance [correction of resosnance] imaging are associated with balance and gait speed. *J Neurol Neurosurg Psychiatr* 2003; **74**: 94–98.
52 Novak V, Haertle M, Zhao P *et al.* White matter hyperintensities and dynamics of postural control. *Magn Reson Imaging* 2009; **27**: 752–759.
53 Silbert LC, Nelson C, Howieson DB, Moore MM, Kaye JA. Impact of white matter hyperintensity volume progression on rate of cognitive and motor decline. *Neurology* 2008; **71**: 108–113.
54 Baloh RW, Ying SH, Jacobson KM. A longitudinal study of gait and balance dysfunction in normal older people. *Arch Neurol* 2003; **60**: 835–839.
55 Corti MC, Baggio G, Sartori L *et al.* White matter lesions and the risk of incident hip fracture in older persons: results from the progetto veneto anziani study. *Arch Intern Med* 2007; **167**: 1745–1751.
56 Blahak C, Baezner H, Pantoni L *et al.* Deep frontal and periventricular age related white matter changes but not basal ganglia and infratentorial hyperintensities are associated with falls: cross sectional results from the ladis study. *J Neurol Neurosurg Psychiatr* 2009; **80**: 608–613.
57 DeCarli C, Fletcher E, Ramey V, Harvey D, Jagust WJ. Anatomical mapping of white matter hyperintensities (WMH): exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. *Stroke* 2005; **36**: 50–55.
58 Rosano C, Brach J, Studenski S, Longstreth WT, Newman AB. Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults. *Neuroepidemiology* 2007; **29**: 193–200.
59 Tullberg M, Fletcher E, DeCarli C *et al.* White matter lesions impair frontal lobe function regardless of their location. *Neurology* 2004; **63**: 246–253.
60 Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res* 2002; **53**: 647–654.
61 Chiu AF, Huang MH, Hsu MH, Liu JL, Chiu JF. Association of urinary incontinence with impaired functional status among older people living in a long-term care setting. *Geriatr Gerontol Int* 2015; **15**: 296–301.
62 Hirono N, Kitagaki H, Kazui H, Hashimoto M, Mori E. Impact of white matter changes on clinical manifestation of Alzheimer's disease: a quantitative study. *Stroke* 2000; **31**: 2182–2188.
63 Samuelsson E, Odeberg J, Stenzelius K *et al.* Effect of pharmacological treatment for urinary incontinence in the elderly and frail elderly: a systematic review. *Geriatr Gerontol Int* 2015; **15**: 521–534.
64 Sakakibara R, Panicker J, Fowler CJ *et al.* Is overactive bladder a brain disease? The pathophysiological role of cerebral white matter in the elderly. *Int J Urol* 2014; **21**: 33–38.
65 Sakakibara R, Panicker J, Fowler CJ *et al.* Vascular incontinence: incontinence in the elderly due to ischemic white matter changes. *Neurol Int* 2012; **4**: e13.
66 Takahashi O, Sakakibara R, Panicker J *et al.* White matter lesions or Alzheimer's disease: which contributes more to overactive bladder and incontinence in elderly adults with dementia? *J Am Geriatr Soc* 2012; **60**: 2370–2371.
67 Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Urinary function in elderly people with and without leukoaraiosis: relation to cognitive and gait function. *J Neurol Neurosurg Psychiatr* 1999; **67**: 658–660.
68 Kuchel GA, Moscufo N, Guttmann CR *et al.* Localization of brain white matter hyperintensities and urinary incontinence in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2009; **64**: 902–909.
69 Sakakibara R, Uchida Y, Ishii K *et al.* Correlation of right frontal hypoperfusion and urinary dysfunction in iNPH: a SPECT study. *Neurourol Urodyn* 2012; **31**: 50–55.
70 Pantoni L, Poggesi A, Basile AM *et al.* Leukoaraiosis predicts hidden global functioning impairment in nondisabled older people: the LADIS (Leukoaraiosis and Disability in the Elderly) Study. *J Am Geriatr Soc* 2006; **54**: 1095–1101.
71 Yoon B, Shim YS, Kim YD *et al.* Correlation between instrumental activities of daily living and white matter hyperintensities in amnestic mild cognitive impairment: results of a cross-sectional study. *Neurol Sci* 2013; **34**: 715–721.
72 Yoon B, Shim YS, Cheong HK *et al.* White matter hyperintensities in mild cognitive impairment: clinical impact of location and interaction with lacunes and medial temporal atrophy. *J Stroke Cerebrovasc Dis* 2014; **23**: e365–e372.
73 Moon SY, Na DL, Seo SW *et al.* Impact of white matter changes on activities of daily living in mild to moderate dementia. *Eur Neurol* 2011; **65**: 223–230.
74 Inzitari D, Pracucci G, Poggesi A *et al.* Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *BMJ* 2009; **339**: b2477.

75 Seo SW, Lee JM, Im K *et al.* Cortical thinning related to periventricular and deep white matter hyperintensities. *Neurobiol Aging* 2012; **33**: 1156–1167.
76 Maillard P, Carmichael O, Fletcher E, Reed B, Mungas D, DeCarli C. Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology* 2012; **79**: 442–448.
77 Inzitari D, Simoni M, Pracucci G *et al.* Risk of rapid global functional decline in elderly patients with severe cerebral age-related white matter changes: the LADIS study. *Arch Intern Med* 2007; **167**: 81–88.
78 Baezner H, Blahak C, Poggesi A *et al.* Association of gait and balance disorders with age-related white matter changes: the LADIS study. *Neurology* 2008; **70**: 935–942.
79 Teodorczuk A, Firbank MJ, Pantoni L *et al.* Relationship between baseline white-matter changes and development of late-life depressive symptoms: 3-year results from the LADIS study. *Psychol Med* 2010; **40**: 603–610.
80 Teodorczuk A, O'Brien JT, Firbank MJ *et al.* White matter changes and late-life depressive symptoms: longitudinal study. *Br J Psychiatry* 2007; **191**: 212–217.
81 Gold DA. An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *J Clin Exp Neuropsychol* 2012; **34**: 11–34.
82 Chen YK, Xiao WM, Li WY *et al.* Neuroimaging indicators of the performance of instrumental activities of daily living in Alzheimer's disease combined with cerebrovascular disease. *Geriatr Gerontol Int* 2015; **15**: 588–593.
83 Kandiah N, Chander R, Zhang A, Yee CC. Cerebral white matter disease is independently associated with BPSD in Alzheimer's disease. *J Neurol Sci* 2014; **337**: 162–166.
84 Berlow YA, Wells WM, Ellison JM, Sung YH, Renshaw PF, Harper DG. Neuropsychiatric correlates of white matter hyperintensities in Alzheimer's disease. *Int J Geriatr Psychiatry* 2010; **25**: 780–788.
85 Palmqvist S, Sarwari A, Wattmo C *et al.* Association between subcortical lesions and behavioral and psychological symptoms in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* 2011; **32**: 417–423.
86 Hsieh CJ, Chang CC, Lin CC. Neuropsychiatric profiles of patients with Alzheimer's disease and vascular dementia in Taiwan. *Int J Geriat Psychiatry* 2009; **24**: 570–577.
87 Caputo M, Monastero R, Mariani E *et al.* Neuropsychiatric symptoms in 921 elderly subjects with dementia: a comparison between vascular and neurodegenerative types. *Acta Psychiatr Scand* 2008; **117**: 455–464.
88 Fuh JL, Wang SJ, Cummings JL. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. *J Neurol Neurosurg Psychiatr* 2005; **76**: 1337–1341.
89 Staekenborg SS, Su T, van Straaten EC *et al.* Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. *J Neurol Neurosurg Psychiatr* 2010; **81**: 547–551.
90 Treiber KA, Lyketsos CG, Corcoran C *et al.* Vascular factors and risk for neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. *Int Psychogeriatr* 2008; **20**: 538–553.
91 van der Flier WM, van Straaten EC, Barkhof F *et al.* Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. *Stroke* 2005; **36**: 2116–2120.
92 Verdelho A, Madureira S, Ferro JM *et al.* Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among nondisabled elderly. The LADIS study. *J Neurol Neurosurg Psychiatr* 2007; **78**: 1325–1330.
93 Jokinen H, Kalska H, Ylikoski R *et al.* MRI-defined subcortical ischemic vascular disease: baseline clinical and neuropsychological findings. The LADIS study. *Cerebrovasc Dis* 2009; **27**: 336–344.
94 Verdelho A, Madureira S, Moleiro C *et al.* White matter changes and diabetes predict cognitive decline in the elderly: the LADIS study. *Neurology* 2010; **75**: 160–167.
95 Jokinen H, Gouw AA, Madureira S *et al.* Incident lacunes influence cognitive decline: the LADIS study. *Neurology* 2011; **76**: 1872–1878.
96 Defrancesco M, Marksteiner J, Deisenhammer E, Kemmler G, Djurdjevic T, Schocke M. Impact of white matter lesions and cognitive deficits on conversion from mild cognitive impairment to Alzheimer's disease. *J Alzheimers Dis* 2013; **34**: 665–672.
97 Prins ND, van Dijk EJ, den Heijer T *et al.* Cerebral white matter lesions and the risk of dementia. *Arch Neurol* 2004; **61**: 1531–1534.
98 Bombois S, Debette S, Bruandet A *et al.* Vascular subcortical hyperintensities predict conversion to vascular and mixed dementia in MCI patients. *Stroke* 2008; **39**: 2046–2051.
99 Staekenborg SS, Koedam EL, Henneman WJ *et al.* Progression of mild cognitive impairment to dementia: contribution of cerebrovascular disease compared with medial temporal lobe atrophy. *Stroke* 2009; **40**: 1269–1274.
100 Brickman AM, Provenzano FA, Muraskin J *et al.* Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer disease in the community. *Arch Neurol* 2012; **69**: 1621–1627.
101 van Straaten EC, Harvey D, Scheltens P *et al.* Periventricular white matter hyperintensities increase the likelihood of progression from amnestic mild cognitive impairment to dementia. *J Neurol* 2008; **255**: 1302–1308.
102 Kantarci K, Weigand SD, Przybelski SA *et al.* Risk of dementia in MCI: combined effect of cerebrovascular disease, volumetric MRI, and 1H MRS. *Neurology* 2009; **72**: 1519–1525.
103 Di Nisio M, Prisciandaro M, Rutjes AWS, Russi I, Maiorini L, Porreca E. Dementia in patients with atrial fibrillation and the value of the Hachinski ischemic score. *Geriatr Gerontol Int* 2015; **15**: 770–777.
104 Bozluolcay M, Andican G, Fırtına S, Erkol G, Konukoglu D. Inflammatory hypothesis as a link between Alzheimer's disease and diabetes mellitus. *Geriatr Gerontol Int* 2015 (Sep 3); doi: 10.1111/ggi.12602; [Epub ahead of print].
105 Saji N, Kimura K, Aoki J, Uemura J, Sakamoto Y. Intracranial Hemorrhage Caused by Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)- Multicenter Retrospective Cohort Study in Japan. *Circ J* 2015; **79**: 1018–1023.
106 Osone A, Arai R, Hakamada R, Shimoda K. Impact of cognitive reserve on the progression of mild cognitive impairment to Alzheimer's disease in Japan. *Geriatr Gerontol Int* 2015; **15**: 428–434.
107 Wang B, He P, Dong B. Association between family functioning and cognitive impairment among Chinese nonagenarians/centenarians. *Geriatr Gerontol Int* 2015; **15**: 1135–1142.
108 Mao HF, Chang LH, Yao G, Chen WY, Huang WW. Indicators of perceived useful dementia care assistive technology: Caregivers' perspectives. *Geriatr Gerontol Int* 2014; **15**: 1049–1057.

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

doi: 10.1111/ggi.12664

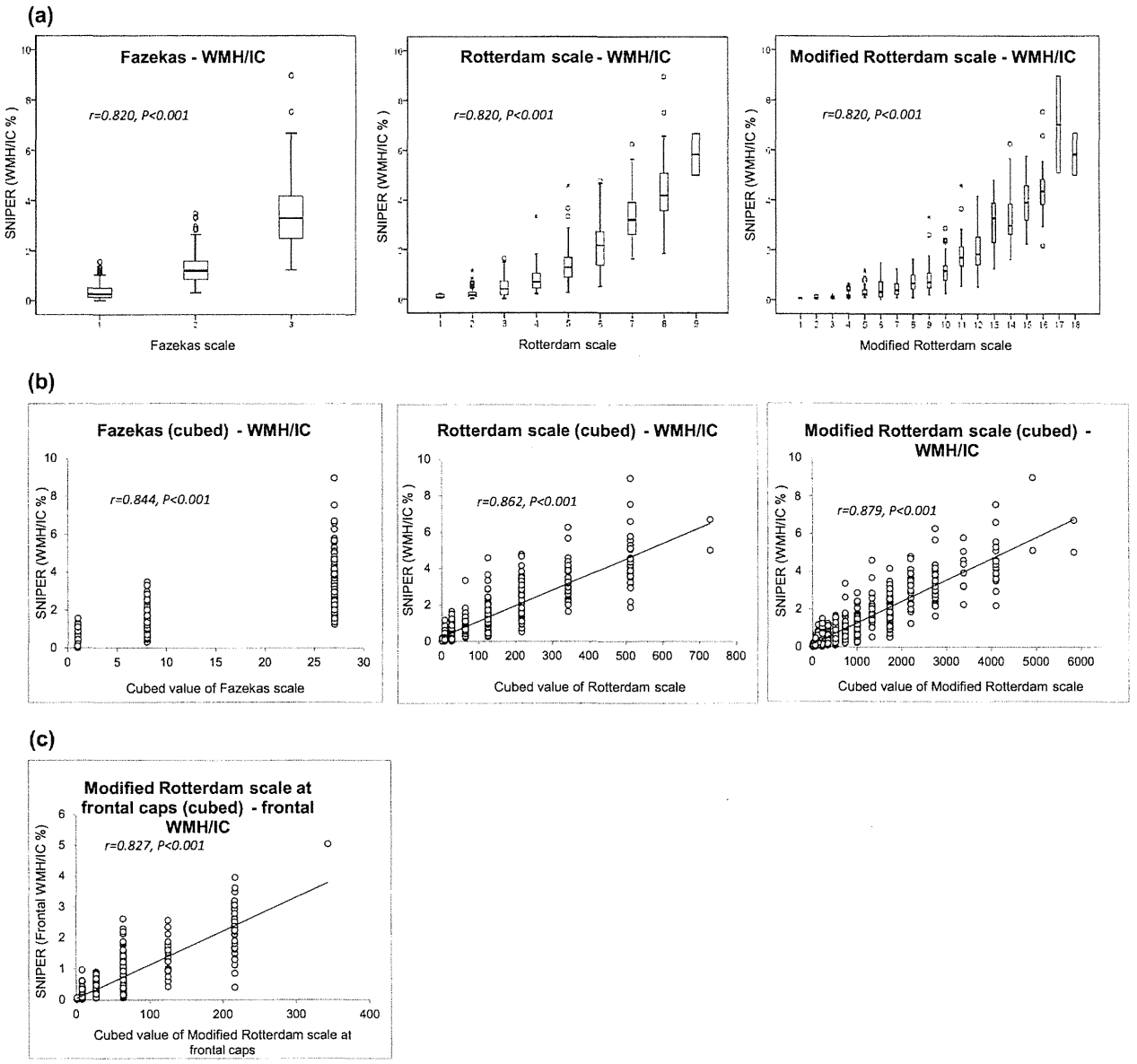

Figure 1 Associations of three visual rating scales with computer-based volumetric analysis. (a) The distribution of the three rating scales and white matter hyperintensity (WMH)/intracranial volume (IC) with box and whisker plots. The *x*-axes are original values of the three visual rating scales. The 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.

Acknowledgments

This study was supported by a grant from the Research Funding for Longevity Sciences (25-6) from the National Center for Geriatrics and Gerontology (NCGG).

Disclosure statement

The authors declare no conflict of interest.

Noriko Ogama,[1,2,3] Naoki Saji,[1] Shumpei Niida,[2] Kenji Toba[1] and Takashi Sakurai[1]

[1]Center for Comprehensive Care and Research on Memory Disorders, [2]Biobank, National Center for Geriatrics and Gerontology, Obu, and [3]Department of Community Healthcare and Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

References

1 Erkinjuntti T, Pohjasvaara T, Pihanen P *et al.* 2001–2011: a decade of the LADIS (Leukoaraiosis And DISability) Study: what have we learned about white matter changes and small-vessel disease? *Cerebrovasc Dis* 2011; **32**: 577–588.

2 Akisaki T, Sakurai T, Takata T *et al.* Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT). *Diabetes Metab Res Rev* 2006; **22**: 376–384.

3 Ogama N, Sakurai T, Shimizu A, Toba K. Regional white matter lesions predict falls in patients with amnestic mild cognitive impairment and Alzheimer's disease. *J Am Med Dir Assoc* 2014; **15**: 36–41.

4 Ogama N, Yoshida M, Nakai T, Niida S, Toba K, Sakurai T. Frontal white matter hyperintensity predicts lower urinary tract dysfunction in older adults with amnestic mild cognitive impairment and Alzheimer's disease. *Geriatr Gerontol Int* 2015 (Jan 22); doi: 10.1111/ggi.12447; [Epub ahead of print].

5 DeCarli C, Fletcher E, Ramey V, Harvey D, Jagust WJ. Anatomical mapping of white matter hyperintensities (WMH): exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. *Stroke* 2005; **36**: 50–55.

6 Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987; **149**: 351–356.

7 de Groot JC, de Leeuw FE, Oudkerk M *et al.* Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol* 2000; **47**: 145–151.

8 Admiraal-Behloul F, van den Heuvel DM, Olofsen H *et al.* Fully automatic segmentation of white matter hyperintensities in MR images of the elderly. *Neuroimage* 2005; **28**: 607–617.

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.

Geriatr Gerontol Int 2015; **15 (Suppl. 1):** *43–47*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Volumetric analyses of cerebral white matter hyperintensity lesions on magnetic resonance imaging in a Japanese population undergoing medical check-up

Yuko Honda,[1] Akio Noguchi,[1] Keisuke Maruyama,[1] Akira Tamura,[2] Isamu Saito,[2] Kazumi Sei,[2] Takamasa Soga,[2] Katsuaki Ushiba,[2] Teruyuki Hirano,[4] Takashi Sakurai[3] and Yoshiaki Shiokawa[1]

Departments of [1]Neurosurgery, [4]Stroke and Cerebrovascular Medicine, Kyorin University School of Medicine, Tokyo, [2]Department of Neurosurgery, Fuji Brain Institute and Hospital, Shizuoka, and [3]The Center for Comprehensive Care and Research on Memory Disorders, National Center for Geriatrics and Gerontology, Aichi, Japan

Aim: To clarify growth patterns, spatial distribution and risk factors of cerebral white matter hyperintensity (WMH) lesions on magnetic resonance imaging.

Methods: We analyzed volumes of cerebral WMH lesions in those who underwent brain magnetic resonance imaging as a hospital-based health check-up in 2012 and 2013 by using a computational quantitative image analysis software (Software for NeuroImage Processing in Experimental Research). After excluding subjects not suitable for volumetric analyses because of pathological brain conditions, a total of 1047 healthy participants (mean age 56.6 years) were included for the analyses. First, the relationship of computational volumetry and conventional qualitative visual evaluation by Shinohara grading was evaluated. Volumes of WMH lesions were analyzed according to age and the different cerebral lobes. Finally, clinical risk factors associated with WMH lesions were assessed.

Results: Volumes of WMH lesions were significantly correlated with Shinohara grading ($P < 0.001$). WMH lesions significantly enlarged with aging ($P < 0.001$) except for the occipital lobe, especially in participants aged 50 years or older. Age and systolic blood pressure were significantly related to volumes of WMH lesions in all the lobes, whereas diastolic blood pressure was not related only in the occipital lobe.

Conclusion: Based on computational quantitative volumetric analyses, cerebral WMH lesions increased with age, and were associated with blood pressure. However, the occipital lobe was the only exception to these findings. **Geriatr Gerontol Int 2015; 15 (Suppl. 1): 43–47.**

Keywords: aging, blood pressure, magnetic resonance imaging, occipital lobe, white matter hyperintensity lesions.

Introduction

White matter hyperintensity (WMH) lesions of the brain on magnetic resonance imaging (MRI) are known as one of the risk factors of stroke.[1] Especially in older adults, WMH lesions can cause various physical disorders including cognitive dysfunction, depression, traumatic injury or aspiration pneumonia.[2–6] The main cause of WMH lesions is known to be small vessel diseases.[7,8] The incidence in the Asian population is high, and that in Japanese older adults is over 70%. WMH lesions even occur in approximately 30% of healthy middle-aged people, related to metabolic syndrome including hypertension, which is widely known as a precondition of stroke.[9] Despite such a significant clinical implication, WMH lesions in the healthy population, which means no inclusion of specific diseases, with a wide range of ages, has been poorly studied. Thus, we evaluated a healthy population carrying out medical check-ups of the brain, and analyzed MRI by using a quantitative image analysis program in an attempt to show the

Accepted for publication 2 October 2015.

Correspondence: Yuko Honda M.D., Department of Neurosurgery, Kyorin University School of Medicine, Shinkawa 6-20-2, Mitaka-shi, Tokyo 181-8611, Japan. Email: yimado-kyr@umin.ac.jp

growth pattern, spatial distribution and clinical risk factors of WMH lesions.

Materials and methods

Participants

A total of 1177 participants who had voluntarily participated in a hospital-based health check-up underwent brain examinations in 2012 and 2013 at Fuji Brain Institute and Hospital, Fujinomiya, Shizuoka, Japan. The subjects not suitable for volumetric analyses because of pathological brain conditions including brain infarctions or neoplasms more than 1 cm in the largest diameter were excluded from the study, because the accuracy of calculation could be compromised. Patients were informed of the study, and the local institutional review board approved the study protocol.

Data collection

We collected MRI and clinical data including age, sex, current history of smoking, habitual alcohol intake, family history of stroke within the second degree, and past history of hypertension, diabetes and dyslipidemia. As physical data, systolic and diastolic blood pressure at hospital visit, body height, bodyweight, and abdominal circumference were obtained, and body mass index was calculated thereafter. As blood examination, complete blood count and plasma levels of glucose, hemoglobin A1c, low- and high-density lipoprotein cholesterol, total cholesterol, and triglyceride were obtained. If there were multiple data during the duration of 2 years of data collection, the first data were selected for the analyses. As MRI, axial images on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images were acquired based on the orbitomeatal line. The MRI investigations were carried out on a 1.5-Tesla whole-body system (Symphony Advance; Siemens, Munich, Germany). The protocol consisted of transversal T2-weighted (TR/TE = 3800/97 ms) sequences, matrix size 195 × 448 and FLAIR (TR/TE/inversion time = 10 000/104/2500 ms) sequences, with a matrix size of 179 × 256, slice thickness of 6.0 mm, gap of 0.9 mm and 19 slices.

We used automatic imaging analysis software to quantitatively measure volumes of WMH lesions (Software for NeuroImage Processing in Experimental Research), which was used in the previous study from the Netherlands.[10] By using this program, volumes of WMH lesions on each lobe and the intracranial capacity were analyzed and shown in cubic centimeters (cm^3).

WMH lesions were also visually assessed by the first author based on Shinohara grading, which consisted of two classifications on T2-weighted MRI as follows.[11] Grading of deep and subcortical WMH (DSWMH); grade 0, absent; grade 1, état criblé (1) T2 high and T1 low or iso, diameter ≤3 mm and boundary sharp, (2) any evidence suggesting état criblé; grade 2, T2 high, T1 iso or partially low, punctate or discrete foci on subcortical and deep white matter; grade 3, T2 high T1 iso (or partially low) confluent foci on deep white matter; and grade 4, T2 high T1 iso (or partially low) confluence widely distributed on most of the white matter. Grading of periventricular hyperintensity (PVH); grade 0, absent or "rims" only; grade 1, localized lesions, such as "caps"; grade 2, extended along the whole periventricular area; grade 3, irregular PVH extending into deep white matter; and grade 4, extending throughout deep and subcortical white matter.

Statistical analyses

The data were analyzed using IBM SPSS Statistics software, version 22 (IBM, Armonk, New York, United States). Volumes of WMH lesions were divided by the intracranial capacity to exclude the influence of individuality for statistical analyses and comparison. Volumes of WMH lesions were analyzed by age groups divided into 10-year age brackets in order to assess the extent and growth of WMH lesions by age. To verify clinical risk factors affecting the WMH lesions, univariate analyses were carried out.

Results

After excluding 130 subjects who were inappropriate for imaging analyses, 1047 participants (609 men and 438 women, mean age 56.5 years) were subsequently evaluated in the present study. Characteristics of the study participants are shown in Table 1. The median volume of WMH lesions was 3.34 cm^3, and the mean volume of whole WMH lesions divided by the total intracranial capacity for all participants was 0.22.

Relationship between volumetry and conventional classification

Volumes of WMH lesions were significantly correlated with conventional qualitative visual evaluation by Shinohara grading of deep and subcortical WMH and periventricular hyperintensity ($P < 0.001$; Fig. 1). Spearman's coefficient of deep and subcortical WMH was 0.745 ($P < 0.001$; Fig. 1a), and that of periventricular hyperintensity was 0.706 ($P < 0.001$; Fig. 1b). However, the deviation from the regression lines enlarged in association with higher Shinohara grade.

Enlargement of WMH lesions by age according to lobes

WMH lesions significantly enlarged with age ($P < 0.001$). The enlargement was prominent especially

Table 1 Baseline characteristics

Characteristics	*n*
n	1047
Age (years)	56.5 ± 9.4
Female sex (%)	41.8
Current smokers (%)	18.0
Habitual alcohol intake (%)	46.6
Body mass index	23.4 ± 3.6
Abdominal circumference/height	0.52 ± 0.06
Hypertension (%)	20.1
Hyperlipidemia (%)	38.4
Diabetes (%)	8.0
Family history of stroke (%)	37.4
Systolic blood pressure (mmHg)	119.7 ± 20.1
Diastolic blood pressure (mmHg)	73.1 ± 11.9
Glucose (mg/dL)	104.5 ± 22.9
Hemoglobin A1c (%)	5.49 ± 0.71
Low-density lipoprotein cholesterol (mg/dL)	128.7 ± 31.4
High-density lipoprotein cholesterol (mg/dL)	63.6 ± 17.8
Total cholesterol (mg/dL)	206.3 ± 34.7
Triglyceride (mg/d)	112.7 ± 77.7

Data are presented as means ± standard deviation or as percentages.

in participants aged in their 50s or older (Fig. 2). According to lobes, more enlargement of WMH lesions was observed in the order of the frontal, the parietal, the temporal and the occipital lobe. After setting the volume of the 30s age group as baseline to compare the difference between lobes, the rate of enlargement was slight only in the occipital lobe (Fig. 3).

Analysis of risk factors related to WMH lesions

In the univariate analyses of WMH lesions, age and systolic blood pressure were significantly related to volumes of WMH lesions in all the lobes. However, the correlation coefficient of them was less than half only in the occipital lobe. Diastolic blood pressure had no statistical significance only in the occipital lobe (Table 2). No other physical data and none of the data from the blood examination were significantly related independently (data not shown).

Discussion

The present computational quantitative volumetric analyses showed that cerebral WMH lesions increased by age, and they were associated with blood pressure. Analyses by Software for NeuroImage Processing in Experimental Research seemed to be appropriate for the

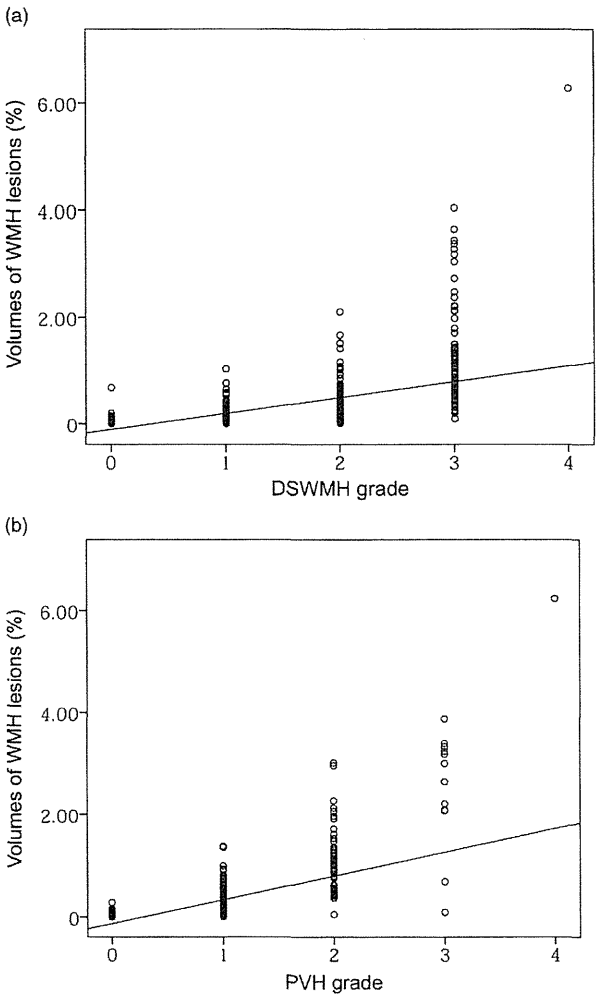

Figure 1 Correlation between volumes of white matter hyperintensity (WMH) lesions by autoanalysis software and Shinohara grading of (a) deep and subcortical WMH (DSWMH) and (b) periventricular hyperintensity (PVL).

evaluation of WMH lesions. A possible explanation of the development of WMH lesions with age might be that the process of aging would be similar to that of systemic arterial sclerosis, as well as cardiovascular disorders, which reportedly showed the marked process of aging after 50 years-of-age, related to small vessel changes.[12]

The occipital lobe was the exception of enlargement of WMH lesions by age, as well as its relationships with blood pressure. The first reason might be the difference of the volumes between the lobes. The second reason might be that the frontal and the parietal lobes have a large area of sparse vascular bed from the cortical branch and the perforators from the intracranial major arteries. The volume of hemodynamic ischemia in the occipital lobe might be anatomically small, and the characteristics of the supplying vessels between the