Print ISSN 1738-1495 / On-line ISSN 2384-0757
Dement Neurocogn Disord 2015;14(3):114-119 / http://dx.doi.org/10.12779/dnd.2015.14.3.114

ORIGINAL ARTICLE

Is the Severity of Dilated Virchow-Robin Spaces Associated with Cognitive Dysfunction?

Eun Hye Jeong,[1] Yong Joo Lee,[2] Sang Joon Kim,[3] Jae-Hong Lee[2]

[1]Department of Neurology, Bundang Jesaeng General Hospital, Seongnam, Korea
Departments of [2]Neurology and [3]Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background and Purpose Dilated Virchow-Robin spaces (dVRS) are not uncommon findings in the normal brain, particularly in the old people, and have been largely regarded as benign lesions. However, there is accumulating evidence that dVRS may serve as an neuroimaging marker of small vessel disease and are associated with cognitive decline. We investigated whether the severity of dVRS would be associated with cognitive dysfunction by comparing the subjects with subjective memory impairment (SMI), mild cognitive impairment (MCI), and Alzheimer's disease (AD). We also examined whether there were differences in the degree of correlation between dVRS and magnetic resonance imaging (MRI) markers of small vessel disease among the three groups.

Methods In this retrospective study, a total of 225 subjects were included: those with SMI (n=65), MCI (n=100), and AD (n=60). We rated the severity of dVRS using the axial MRI slice containing the greatest number of dVRS in the basal ganglia (dVRS-BG) and in the deep white matter (dVRS-WM), separately. We also assessed baseline characteristics including vascular risk factors and MRI markers of small vessel disease such as white matter hyperintensities (WMH), lacunar infarcts and microbleeds.

Results A cumulative logit model revealed that the severity of cognitive dysfunction was associated with age (p<0.001), hypertension (p=0.006), diabetes mellitus (p=0.042), the severity of dVRS-BG (p=0.001), the severity of WMH (p=0.074) and the presence of lacunar infarcts (p<0.001) and microbleeds (p=0.003) in univariate analysis. However, after adjusting for other confounding variables, the severity of dVRS-BG was not a significant discriminating factor among subjects with SMI, MCI, and AD. Spearman's correlation analysis showed a trend that the correlation between the severity of dVRS-BG and the severity of WMH became more prominent in subjects with AD than in those with MCI or SMI (r=0.191 in SMI; r=0.284 in MCI; r=0.312 in AD), and the same is true of the severity of dVRS-BG and the number of lacunar infarcts.

Conclusions The severity of dVRS was associated with cognitive dysfunction, which appeared to be confounded by other well-known risk factors. The correlation between dVRS-BG and small vessel disease markers tended to be more significant with the advancement of cognitive impairment. These results suggest that severe dVRS may reflect cerebral small vessel disease and contribute to cognitive impairment.

Key Words dilated Virchow-Robin spaces, cognition, Alzheimer's disease, mild cognitive impairment, white matter hyperintensities, small vessel disease.

Received: September 7, 2015 **Revised:** September 10, 2015 **Accepted:** September 10, 2015

Correspondence: Jae-Hong Lee, MD, PhD, Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3446, **Fax:** +82-2-474-4691, **E-mail:** jhlee@amc.seoul.kr

INTRODUCTION

Virchow-Robin spaces (VRS) are perivascular spaces surrounding the perforating cerebral arteries or arterioles.[1,2] They distribute throughout the subarachnoid space to the brain parenchyma. Solutes from the brain parenchyma and lymphatics are drained into VRS, but VRS themselves do not have direct communication with the subarachnoid space.[3] Dilated VRS (dVRS) are easily detectable by magnetic resonance imaging (MRI), usually in the basal ganglia (BG) at the level of the anterior commissure and in the deep white matter (WM), along the penetrating vessels.[4] They appear as non-enhancing, high T2 and low T1 signals with iso-signal intensities

relative to cerebrospinal fluid (CSF), and sometimes may resemble small lacunar infarct lesions.

dVRS are commonly detected in the normal brain, particularly in the elderly. Because dVRS seldom lead to tissue damage in the surrounding parenchyma, they have been regarded as benign variants.[5] However, their exact role and pathogenesis is still controversial. The dilation may be caused by an alteration in the blood brain barrier,[6] abnormal interstitial fluid drainage,[7] or segmental angiitis.[8]

Recently, there is accumulating evidence that dVRS are associated with some pathological conditions, such as stroke, small vessel disease,[9] dementia,[10] and multiple sclerosis.[11] dVRS were reported to be associated with deterioration of non-verbal reasoning and visuospatial ability in healthy elderly men.[12] A large population-based prospective study showed that a high degree of dVRS was associated with increased risk of dementia and higher rate of cognitive decline.[10] The parenchymal amyloid is believed to be drained with interstitial fluid along the perivascular pathway.[13] dVRS may somehow affect the clearance mechanism of brain amyloid, contributing to Alzheimer's disease (AD).

However, there have been few studies addressing the implication of dVRS in the development of AD. Therefore, the purpose of our study was to investigate the association of dVRS with various levels of cognitive dysfunction and the relationship of dVRS to cerebral small vessel disease, particularly in AD patients with cerebrovascular lesion.

METHODS

Subjects

In this retrospective study, we reviewed the patients who visited the memory disorder clinic of Asan Medical Center, Seoul, Korea between March, 2009 and August, 2012. A total of 225 subjects were included: those with subjective memory impairment (SMI) (*n*=65), mild cognitive impairment (MCI) (*n*=100), and AD (*n*=60). All subjects underwent detailed history taking, physical and neurologic examinations, neuropsychological assessment and MRI scan. For SMI, we included subjects with sustained subjective memory complaints, but normal age-, gender-, and education-adjusted cognitive performance in Seoul Neuropsychological Screening Battery.[14] Patients who fulfilled the Petersen's MCI criteria were enrolled in the MCI group.[15] The diagnosis of dementia was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition.[16] The diagnosis of AD was made on the basis of criteria for possible and probable AD proposed by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.[17]

Clinical parameters

Information on age, sex, the Korean version of Mini-Mental State Examination (K-MMSE) score, and vascular risk factors was collected. Investigation was done on vascular risk factors including hypertension (previously diagnosed and treated, or systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg), diabetes mellitus (previously diagnosed and treated, or fasting blood glucose ≥126 mg/dL and/or postprandial 2 hour glucose ≥200 mg/dL), hyperlipidemia (previously diagnosed and treated, or total cholesterol ≥200 mg/dL or low density lipoprotein-cholesterol ≥130 mg/dL), and history of coronary artery disease and atrial fibrillation.

Rating of dVRS and other MRI parameters

All subjects had MRI scan using Achieva 1.5-T MRI (Philips, Eindhoven, the Netherlands). The imaging protocol included the axial sequences with 5.0 mm-thickness of T2-weighted [repetition time (TR)/echo time (TE) 3018.7/100.0 msec], fluid attenuated inversion recovery (FLAIR; TR/TE

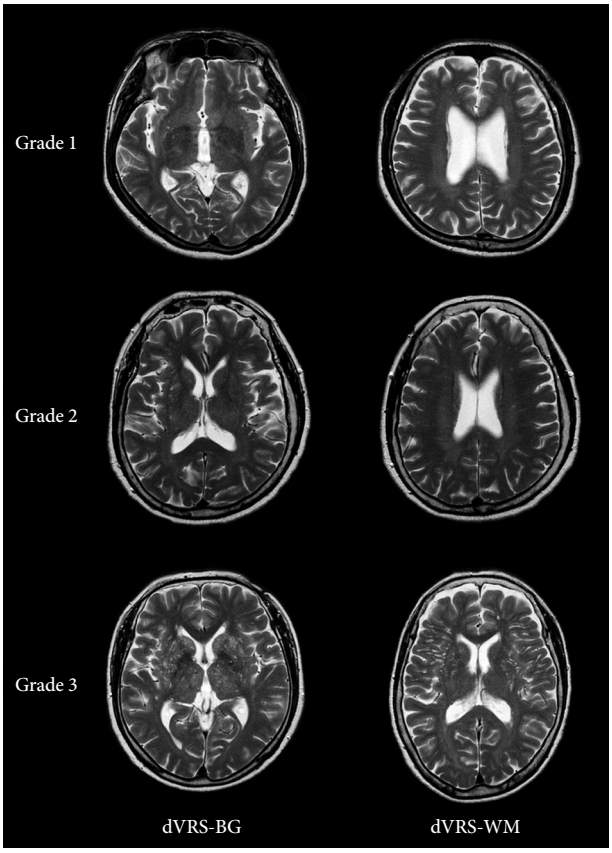

Fig. 1. Representative MRI scans showing the severity of dilated Virchow-Robin spaces in the basal ganglia (dVRS-BG) and deep white matter (dVRS-WM).

11000.0/140.0 msec), gradient echo (GRE; TR/TE 400.0/30.0 msec) images and coronal sequences with 3.0 mm-thickness of T1-weighted images (TR/TE 10.0/3.7 msec).

dVRS were defined as CSF-like signal lesions (hypointense on T1 and hyperintense on T2) of round, ovoid, or linear shape with smooth delineated contours. Each of the axial slices was initially searched to identify the slice containing the greatest number of dVRS in the BG and deep WM (Fig. 1). Then, we rated the severity of dVRS using an arbitrary three-level scale from the slice containing the greatest number of dVRS in the BG (dVRS-BG) and deep WM (dVRS-WM), respectively. The grading of dVRS was defined as follows: 'grade 1' when there were less than 10 dVRS; 'grade 2' when there were between 10 and 20 dVRS; 'grade 3' when there were more than 20 dVRS (Fig. 1).

We also assessed MRI markers of small vessel disease such as white matter hyperintensities (WMH), lacunar infarcts and microbleeds. The degree of WMH severity was rated on the axial FLAIR images using a Clinical Research for Dementia of South Korea rating scale.[18] Each periventricular and deep WM changes were rated separately and the results were combined to give a final score of minimal, moderate, or severe. Lacunar infarcts were defined as small lesions less than 15 mm-diameter with high signal intensities on T2- and low signal intensities on T1-weighted images, and the perilesional halo on FLAIR images. Microbleeds were defined as round-shaped and homogeneously low signal lesions with less than 10 mm-diameter on GRE images.[19] Lacunar infarcts and microbleeds were rated by two methods to use adequate variables according to each of the statistical analyses: counting the number or the presence of the lesions.

Statistical analysis

The differences of demographic and clinical characteristics among the three groups were analyzed by analysis of variance or Kruskal-Wallis test for age and K-MMSE score, and by chi-square test or Fisher's exact test for sex and the presence of vascular risk factors. The statistical significance was defined as $p<0.05$. For the evaluation of the association of the severity of dVRS with cognitive function, we used a cumulative logit model in which the severity of cognitive dysfunction was a dependent variable, subdivided as the groups of subjects with SMI, MCI, and AD. The statistical significance was defined as $p<0.2$ in univariate analysis, and $p<0.05$ in multivariable analysis. For the comparison of the degree of the correlation between dVRS and MRI markers of small vessel disease among the three groups, Spearman's correlation analysis was done and the statistical significance was defined as $p<0.05$. A commercial software package (SPSS, version 19.0, IBM, Armonk, NY, USA) was used for statistical analysis.

RESULTS

Table 1 shows the demographic characteristics and vascular risk factors of subjects with SMI, MCI, and AD. The mean age of the AD group was significantly higher than the other groups, followed by the MCI group and the SMI group (74.0±8.6 years vs. 68.0±10.3 years vs. 62.0±8.7 years, $p<0.001$). The mean K-MMSE score was significantly lower in the AD group than the other groups, followed by the MCI group and the SMI group (18.7±5.1 vs. 24.6±4.0 vs. 28.2±2.3, $p<0.001$). The prevalence of hypertension was higher in the AD group compared with the SMI group (53.3% vs. 29.2%, $p=0.018$). There were no significant differences among the three groups in terms of sex, and the prevalence of diabetes mellitus, hyperlipidemia, and cardiac disease. A cumulative logit model revealed that the severity of cognitive dysfunction was associated with age [odds ratio (OR) 1.09, 95% confidential interval (CI) 1.06−1.12; $p<0.001$], hypertension (OR 2.003, 95% CI 1.217−3.296; $p=0.006$), diabetes mellitus (OR 1.909, 95% CI

Table 1. Demographic and clinical characteristics of the subjects

	Total	SMI	MCI	AD	*p* value
n	225	65	100	60	
Age (year)	67.9±10.4	62.0±8.7	68.0±10.3	74.0±8.6	<0.001*
Female	157 (69.8)	47 (72.3)	73 (73.0)	37 (61.7)	0.279
K-MMSE	24.1±5.3	28.2±2.3	24.6±4.0	18.7±5.1	<0.001*
Hypertension	97 (43.1)	19 (29.2)	46 (46.0)	32 (53.3)	0.018†
Diabetes mellitus	42 (18.7)	7 (10.8)	20 (20.0)	15 (25.0)	0.112
Hyperlipidemia	52 (23.1)	15 (23.1)	23 (23.0)	14 (23.3)	0.999
Cardiac disease	20 (8.9)	6 (9.2)	5 (5.0)	9 (15.0)	0.098

Values are presented as mean±standard deviation or as number (percentage) of subjects.
*$p<0.05$, analysis of variance or Kruskal-Wallis test, †$p<0.05$, chi-square test or Fisher's exact test.
AD: Alzheimer's disease, K-MMSE: Korean version of Mini-Mental State Examination, MCI: mild cognitive impairment, SMI: subjective memory impairment.

Table 2. Risk factors for the severity of cognitive dysfunction

	Univariate analysis*		Multivariable analysis*	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.09 (1.06–1.12)	<0.001†	1.074 (1.04–1.11)	<0.0001‡
Sex				
Male	1.00			
Female	0.707 (0.414–1.207)	0.204		
Hypertension				
No	1.00		1.00	
Yes	2.003 (1.217–3.296)	0.006†	1.19 (0.68–2.06)	0.5436
Diabetes mellitus				
No	1.00		1.00	
Yes	1.909 (1.023–3.560)	0.042†	1.22 (0.62–2.41)	0.5674
Hyperlipidemia				
No	1.00			
Yes	1.010 (0.567–1.796)	0.974		
Cardiac disease				
No	1.00			
Yes	1.695 (0.681–4.222)	0.257		
dVRS-BG				
Grade 1	1.00	0.0015†	1.00	0.239
Grade 2	2.46 (1.37–4.43)	0.003†	1.67 (0.89–3.09)	0.1099
Grade 3	3.64 (1.64–8.06)	0.001†	1.24 (0.49–3.11)	0.6511
dVRS-WM				
Grade 1	1.00	0.9167		
Grade 2	1.15 (0.60–2.18)	0.677		
Grade 3	1.09 (0.58–2.02)	0.793		
WMH				
Minimal	1.00	0.0009†	1.00	0.6944
Moderate	2.93 (1.59–5.41)	0.001†	1.28 (0.65–2.54)	0.4763
Severe	2.93 (0.90–9.54)	0.074†	1.48 (0.41–5.32)	0.5491
Lacunar infarcts				
No	1.00		1.00	
Yes	2.63 (1.54–4.49)	<0.001†	1.19 (0.63–2.24)	0.5934
Microbleeds				
No	1.00		1.00	
Yes	2.45 (1.36–4.41)	0.003†	1.31 (0.69–2.50)	0.4131

*The severity of cognitive dysfunction is a dependent variable, subdivided as the groups of subjects with SMI, MCI, and AD, †$p<0.2$, ‡$p<0.05$, cumulative logit model.
AD: Alzheimer's disease, CI: confidential interval, dVRS-BG: dilated Virchow-Robin spaces in the basal ganglia, dVRS-WM: dilated Virchow-Robin spaces in the deep white matter, MCI: mild cognitive impairment, OR: odds ratio, SMI: subjective memory impairment, WMH: white matter hyperintensities.

1.023−3.560; p=0.042), the severity of dVRS-BG (OR 3.64, 95% CI 1.64−8.06; p=0.001), the severity of WMH (OR 2.93, 95% CI 0.90−9.54; p=0.074) and the presence of lacunar infarcts (OR 2.63, 95% CI 1.54−4.49; p<0.001) and microbleeds (OR 2.45, 95% CI 1.36−4.41; p=0.003) in univariate analysis (Table 2). However, after adjusting for other confounding variables, the severity of dVRS-BG was not a significant discriminating factor among subjects with SMI, MCI, and AD (OR 1.24, 95% CI 0.49−3.11; p=0.651). Spearman's correlation analysis showed a trend that the correlation between the severity of dVRS-BG and the severity of WMH became more prominent in subjects with AD than in those with MCI or SMI (r=0.191, p=0.128 in SMI; r=0.284, p=0.004 in MCI; r=0.312, p=0.015 in AD) (Table 3). The same is true of the relationship between dVRS-BG and lacunar infarcts (r=0.390, p=0.001 in SMI; r=0.306, p=0.002 in MCI; r=0.395, p=0.002 in AD).

Table 3. Correlation between the severity of dVRS and MRI markers of small vessel disease among subjects with SMI, MCI, and AD

	SMI		MCI		AD	
	Correlation coefficient (*r*)	*p* value	Correlation coefficient (*r*)	*p* value	Correlation coefficient (*r*)	*p* value
dVRS-BG†						
WMH*	0.191	0.128	0.284	0.004†	0.312	0.015†
Lacunar infarcts*	0.390	0.001†	0.306	0.002†	0.395	0.002†
Microbleeds	0.254	0.041†	0.243	0.015†	0.142	0.278
dVRS-WM						
WMH	0.025	0.843	-0.027	0.788	-0.166	0.205
Lacunar infarcts	0.075	0.553	0.148	0.141	0.009	0.946
Microbleeds	-0.009	0.942	0.028	0.780	0.145	0.268

*Correlation coefficient (*r*) tend to increase more in the AD group than in the MCI or SMI groups, †$p<0.05$, Spearman's correlation analysis.
AD: Alzheimer's disease, dVRS: dilated Virchow-Robin spaces, dVRS-BG: dilated Virchow-Robin spaces in the basal ganglia, dVRS-WM: dilated Virchow-Robin spaces in the deep white matter, MCI: mild cognitive impairment, MRI: magnetic resonance imaging, SMI: subjective memory impairment, WMH: white matter hyperintensities.

DISCUSSION

In this study, we correlated the severity of cognitive dysfunction with various risk factors including the severity of dVRS. Univariate analysis revealed that the severity of dVRS-BG was a risk factor for cognitive dysfunction along with age, hypertension, diabetes mellitus, severity of WMH and the presence of lacunar infarcts and microbleeds. Multivariable analysis using these factors as covariates, however, showed that the severity of dVRS-BG may affect the cognitive dysfunction in association with other risk factors such as WMH. One study reported dVRS in a higher frequency in patients with AD and MCI than normal controls (F=16.50, $p<0.001$; AD>MCI>normal).[20] However, dVRS were associated with leukoaraiosis ($r=0.55$, $p<0.001$), indicating that small vessel pathology may be a confounding factor. Another study reported that dVRS were associated with increased risk of dementia including pure vascular dementia during a 4-year follow up period [hazard ratio (HR)=5.8, 95% CI 1.2−28.4, $p=0.03$ for dVRS-BG; HR=9.8, 95% CI 1.7−55.3, $p=0.01$ for dVRS-WM],[10] suggesting that the increased risk of dementia may also be due to vascular pathology. Taken together, dVRS themselves are not directly associated with cognitive dysfunction. Rather, dVRS may contribute to dementia through cerebrovascular pathology, particularly small vessel disease.

In regard to the relationship between dVRS and small vessel disease markers, our study exhibited a close correlation between dVRS-BG and WMH or lacunar infarcts. This correlation was more prominent in subjects with AD than in those with MCI or SMI, which is in consistent with the previous report where the dVRS were correlated with lacunes and WMH only in AD patients ($r=0.3$, $p<0.01$), not in normal elderly controls.[21] Our results suggest that dVRS themselves may not be a definite risk factor for AD, but may affect cognitive dysfunction by contributing to small vessel disease pathology, independent of AD pathology. In another study comparing dVRS in patients with AD, vascular dementia, or frontotemporal dementia, there was no significant difference of dVRS between normal controls and AD patients but dVRS-BG were significantly associated with vascular dementia patients as compared to AD patients ($p<0.001$) or normal controls ($p<0.001$).[22] This also supports the findings of our study in that dVRS can be a marker of cerebral small vessel disease.

In contrast to dVRS-BG, dVRS-WM were neither associated with cognitive dysfunction, nor with WMH or lacunar infarcts in our study, which is consistent with previous studies that dVRS in the BG rather than in WM were related to a higher rate of cognitive decline[10] and that dVRS-WM showed no difference between AD patients and vascular dementia patients.[22,23] An autopsy based study revealed that small lacunes in the BG and thalamus correlated with cognitive decline in elderly patients, while lacunes in the deep WM did not.[24] According to another study, arteriosclerosis in AD initially affects the BG rather than WM,[25] and arteriosclerosis has been shown to be related to dVRS in the BG.[26] Therefore, the different results between dVRS-BG and dVRS-WM may be explained by a different underlying pathogenesis.

The limitation of our study is the use of an arbitrary visual scale for measurement of dVRS. However, this problem was inherent in those studies dealing with dVRS because there is no standardized method available for use. Previous studies also used their own scales. A recent work using a verified scale lacked correlation with pathologic confirmation.[27] Instead, we devised a scale with reference to previous studies, combining both qualitative and quantitative aspects. Secondly, our study is a cross-sectional one which hinders the inference of tempo-

ral relationship and causality between dVRS and dementia. Longitudinal prospective study involving a larger number of subjects is warranted to further explore the implication of dVRS in the context of AD dementia.

In conclusion, the severity of dVRS was associated with cognitive dysfunction, which appeared to be confounded by other well-known risk factors. The correlation between dVRS-BG and MRI markers of small vessel disease was more significant in subjects with AD. These results suggest that dVRS may be considered as another marker of small vessel disease and implicated in cognitive decline.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgements

This study was supported by a grant from the Korea Institute of Medicine (KIOM) (#2011-0569).

REFERENCES

1. Kwee RM, Kwee TC. Virchow-Robin spaces at MR imaging. *Radiographics* 2007;27:1071-1086.
2. Rouhl RP, van Oostenbrugge RJ, Knottnerus IL, Staals JE, Lodder J. Virchow-Robin spaces relate to cerebral small vessel disease severity. *J Neurol* 2008;255:692-696.
3. Schley D, Carare-Nnadi R, Please CP, Perry VH, Weller RO. Mechanisms to explain the reverse perivascular transport of solutes out of the brain. *J Theor Biol* 2006;238:962-974.
4. Zhu YC, Dufouil C, Mazoyer B, Soumaré A, Ricolfi F, Tzourio C, et al. Frequency and location of dilated Virchow-Robin spaces in elderly people: a population-based 3D MR imaging study. *AJNR Am J Neuroradiol* 2011;32:709-713.
5. Jungreis CA, Kanal E, Hirsch WL, Martinez AJ, Moossy J. Normal perivascular spaces mimicking lacunar infarction: MR imaging. *Radiology* 1988;169:101-104.
6. Benhaïem-Sigaux N, Gray F, Gherardi R, Roucayrol AM, Poirier J. Expanding cerebellar lacunes due to dilatation of the perivascular space associated with Binswanger's subcortical arteriosclerotic encephalopathy. *Stroke* 1987;18:1087-1092.
7. Pollock H, Hutchings M, Weller RO, Zhang ET. Perivascular spaces in the basal ganglia of the human brain: their relationship to lacunes. *J Anat* 1997;191(Pt 3):337-346.
8. Homeyer P, Cornu P, Lacomblez L, Chiras J, Derouesné C. A special form of cerebral lacunae: expanding lacunae. *J Neurol Neurosurg Psychiatry* 1996;61:200-202.
9. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. *Stroke* 2010;41:450-454.
10. Zhu YC, Dufouil C, Soumaré A, Mazoyer B, Chabriat H, Tzourio C. High degree of dilated Virchow-Robin spaces on MRI is associated with increased risk of dementia. *J Alzheimers Dis* 2010;22:663-672.
11. Wuerfel J, Haertle M, Waiczies H, Tysiak E, Bechmann I, Wernecke KD, et al. Perivascular spaces--MRI marker of inflammatory activity in the brain? *Brain* 2008;131(Pt 9):2332-2340.
12. Maclullich AM, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *J Neurol Neurosurg Psychiatry* 2004;75:1519-1523.
13. Weller RO, Yow HY, Preston SD, Mazanti I, Nicoll JA. Cerebrovascular disease is a major factor in the failure of elimination of Abeta from the aging human brain: implications for therapy of Alzheimer's disease. *Ann N Y Acad Sci* 2002;977:162-168.
14. Kang YW, Na DL. *Seoul neuropsychological screening battery*. Incheon: Human Brain Research & Consulting Co., 2003.
15. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256:183-194.
16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association, 2000.
17. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.
18. Moon SY, Na DL, Seo SW, Lee JY, Ku BD, Kim SY, et al. Impact of white matter changes on activities of daily living in mild to moderate dementia. *Eur Neurol* 2011;65:223-230.
19. Seo SW, Im K, Lee JM, Kim YH, Kim ST, Kim SY, et al. Cortical thickness in single- versus multiple-domain amnestic mild cognitive impairment. *Neuroimage* 2007;36:289-297.
20. Chen W, Song X, Zhang Y; Alzheimer's Disease Neuroimaging Initiative. Assessment of the Virchow-Robin Spaces in Alzheimer disease, mild cognitive impairment, and normal aging, using high-field MR imaging. *AJNR Am J Neuroradiol* 2011;32:1490-1495.
21. Ramirez J, Berezuk C, McNeely AA, Scott CJ, Gao F, Black SE. Visible Virchow-Robin spaces on magnetic resonance imaging of Alzheimer's disease patients and normal elderly from the Sunnybrook Dementia Study. *J Alzheimers Dis* 2015;43:415-424.
22. Patankar TF, Mitra D, Varma A, Snowden J, Neary D, Jackson A. Dilatation of the Virchow-Robin space is a sensitive indicator of cerebral microvascular disease: study in elderly patients with dementia. *AJNR Am J Neuroradiol* 2005;26:1512-1520.
23. Hansen TP, Cain J, Thomas O, Jackson A. Dilated perivascular spaces in the Basal Ganglia are a biomarker of small-vessel disease in a very elderly population with dementia. *AJNR Am J Neuroradiol* 2015;36:893-898.
24. Gold G, Kövari E, Herrmann FR, Canuto A, Hof PR, Michel JP. Cognitive consequences of thalamic, basal ganglia, and deep white matter lacunes in brain aging and dementia. *Stroke* 2005;36:1184-1188.
25. Weller RO, Boche D, Nicoll JA. Microvasculature changes and cerebral amyloid angiopathy in Alzheimer's disease and their potential impact on therapy. *Acta Neuropathol* 2009;118:87-102.
26. van Swieten JC, van den Hout JH, van Ketel BA, Hijdra A, Wokke JH, van Gijn J. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. *Brain* 1991;114(Pt 2):761-774.
27. Adams HH, Cavalieri M, Verhaaren BF, Bos D, van der Lugt A, Enzinger C, et al. Rating method for dilated Virchow-Robin spaces on magnetic resonance imaging. *Stroke* 2013;44:1732-1735.