Prevalence and Clinicoradiological Analyses of Patients with Alzheimer Disease Coexisting Multiple Microbleeds

Junpei Nagasawa, MD,* Tetsuhito Kiyozuka, MD,† and Ken Ikeda, MD, PhD*

Background: Pathologic findings of cerebral amyloid angiopathy (CAA) and Alzheimer disease (AD) coexist frequently. Both diseases are associated with β-amyloid deposition and dementia. We aimed to evaluate frequency and clinicoradiological profile of AD patients with multiple microbleeds (MBs). *Methods:* We reviewed clinical records and magnetic resonance imaging (MRI) findings in patients with probable AD diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria from 2009 to 2012. Brain MRI was performed at 1.5-T superconducting system, including T2*-weighted gradient-echo imaging. MBs were defined as rounded, hypointense foci less than or equal to 10 mm in size in the brain parenchyma. MBs topography was divided into the lobar (L) and the deep/infratentorial (D/I) region. Multiple MBs were defined as the number greater than or equal to 8 in the L and the D/I territory, respectively. White matter hyperintensities (WMHs) were assessed using the age-related white matter changes scale. Clinicoradiological findings were examined for 1 year. Prevalence and clinicoradiological profiles were studied in patients with multiple L or D/I MBs. *Results:* Five hundred fifty patients (238 men and 321 women) participated in the present study. Mean age (standard deviation) was 78.4 (7.7) years, 78.3 (8.1) years in men and 78.6 (7.5) years in women. A total of 133 patients (55 men and 78 women) had at least 1 MB. Prevalence of MB ≥ 1 was 24%, 23 in men and 25 in women. The ratio of L and D/I MBs were 1.1, .6 in men and 1.8 in women. Multiple MBs were detected in 93 patients (17%), 38 (16%) men and 55 (17%) in women. L distribution was found in 49 patients (9%), 15 men (6%) and 34 women (11%), and D/I distribution in 44 patients (8%), 23 men (10%) and 21 women (7%). Multiple L MBs was associated with faster progression of dementia, cerebral hemorrhage, and increased number of MBs. Multiple D/I MBs were linked to hypertension and WMH scores. *Conclusions:* The present study indicated that the prevalence of multiple MBs was 17% in Japanese AD patients. The clinicoradiological profile suggested severe degree of CAA in patients with multiple L MBs (9%) and hypertension and aged changes in patients with multiple D/I MBs (8%). T2*-weighted imaging is a useful tool for evaluating degree of CAA and hypertensive vascular changes. We should pay more attention to management and care in AD patients with multiple MBs. **Key Words:** Alzheimer's disease—Cerebral microbleed—Microbleed topography—Cerebral amyloid angiopathy—Atherosclerosis—Neurological profile.

From the *Department of Neurology, Toho University Omori Medical Center; and †Department of Neurology, Mishuku Hospital, Tokyo, Japan.

Received May 16, 2014; accepted May 24, 2014.

Address correspondence to Ken Ikeda, MD, PhD, Department of Neurology, Toho University Omori Medical Center, 6-11-1, Omorinishi, Otaku, Tokyo, 143-8541, Japan. E-mail: keni@med.toho-u.ac.jp.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.05.036

Introduction

Alzheimer disease (AD) is the usual cause of dementia in the elderly. The pathologic hallmarks reveal neuritic plaques and neurofibrillary tangles.[1] Furthermore, intravascular amyloid β deposition is demonstrated at autopsy in 70%-98% of AD patients.[2] Cerebral microbleeds (MBs) is detected on gradient-echo T2*-weighted magnetic resonance imaging (MRI) and the histologic finding is characterized by the presence of hemosiderin around small vessels, suggesting hypertensive small vessel disease and cerebral amyloid angiopathy (CAA).[3,4] MBs are exposed frequently in patients with stroke[4,5] and cognitive dysfunction, including AD,[6-9] vascular dementia,[10] and subnormal cognitive function.[11] Most of the previous studies included many AD patients with only one or a few MBs.[6,12-17] A subgroup of AD patients shows many MBs occasionally.[8] Little is known about the prevalence and the clinical significance in Asian AD patients with multiple MBs. Here, we aimed to elucidate the frequency and the clinicoradiological profile in Japanese AD patients coexisting multiple MBs.

Methods

Study Patients

We analyzed consecutive patients with AD who visited the outpatient department of neurology between January 2009 and December 2012. The diagnosis of AD was made by experienced neurologists based on the clinical history and examination, according to DSM-IV criteria and NINCDS/ADRDA criteria.[1] The present study was approved by Ethical Committee of Toho University Omori Medical Center. (No:25-242)

Radiological Assessment on MRI

MRI was produced by a 1.5-T superconducting system. Twenty-one contiguous axial 5-mm-thick slices (interslice gaps, .5 mm) were performed with the following gradient-echo T2*-weighted pulse sequences: repetition time, 667 milliseconds; echo time, 23 milliseconds; field of view, 230 × 230 mm; matrix 256 × 256. T1-weighted, T2-weighted, and fluid-attenuated inversion recovery images were also obtained. MBs were defined on gradient-echo T2*-weighted imaging as a round area of signal loss less than or equal to 10 mm in diameter. Hypointensity signal areas due to calcification in the globus pallidus and flow void artifact in the cerebral pial vessel were carefully excluded. Subject with MBs were divided into 2 groups by the location of MBs.[18] The lobar (L) MB topography showed MBs in the cerebral cortex, the subcortical white matter, or the periventricular white matter (Fig 1). The deep (D) and the infratentorial (I) MB topography disclosed MBs in the basal ganglia, the thalamus, the brain stem, and the cerebellum (Fig 2). Cerebral white matter hyperintensities (WMHs) on fluid-attenuated inversion recovery imaging were assessed using the age-related white matter changes scale.[19] The age-related WMH was graded from 0 to 3 score (none, punctuate, early confluent, and confluent) in 5 regions, each left and right, adding up to a total range from 0 to 30. Two experienced neurologists and 1 experienced neuroradiologist reviewed the MRI, including the number and location of MBs and WMH, blinded to the clinical data of all patients.

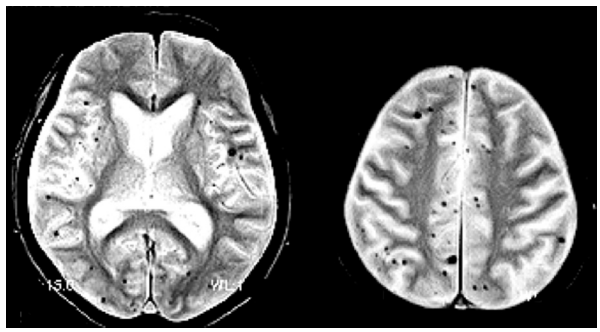

Figure 1. *Multiple lobar microbleeds. T2*-weighted imaging showed round-shaped hypointense foci in the cerebral cortex and the subcortical region.*

Clinical Assessment

The clinical records were reviewed retrospectively for age, sex, Mini-Mental State Examination (MMSE) score, cardiovascular disease (CVD) risk factors, and medication of antiplatelet or anticoagulant agents. CVD risk factors were analyzed on the following 5 items: current smoker; hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) or currently under treatment; diabetes mellitus (fasting blood sugar ≥ 126 mg/dL or hemoglobin A_{1c} ≥ 6.5%) or currently under treatment; dyslipidemia (serum low-density lipoprotein cholesterol ≥ 140 mg/dL or high-density lipoprotein cholesterol < 40 mg/dL) or currently under treatment; and prior history of stroke. Fasting blood samples were obtained from the antecubital vein. Clinicoradiological findings of MMSE and MBs were examined for 1 year. We defined faster progression of dementia as the MMSE decline per year greater than or equal to 6 points.

Prevalence and Clinicoradiological Evaluation of Multiple MBs

Multiple MBs were defined as the number greater than or equal 8, according of the previous study of Goos et al.[8] The number of MBs was counted in the L and the D/I territory, respectively. The prevalence and the clinicoradiological profile were analyzed in patients with multiple L or D/I MBs.

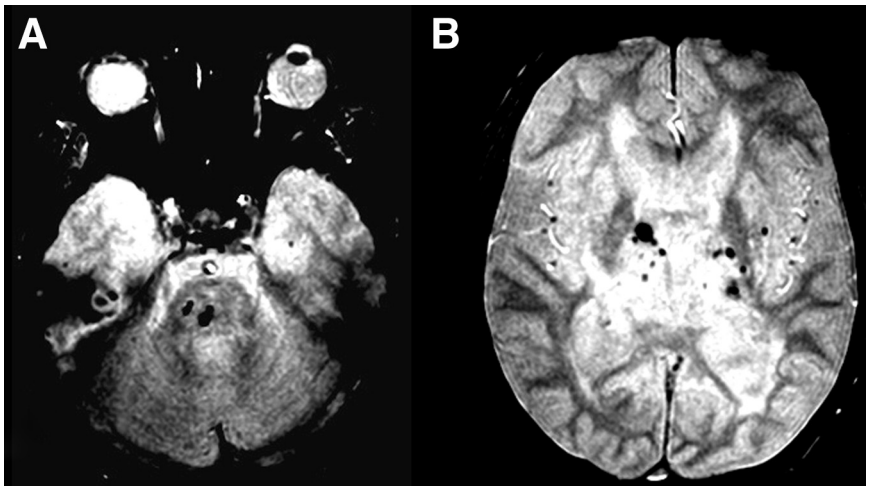

Figure 2. *Multiple deep and infratentorial microbleeds. (A) Infratentorial view. (B) Deep regional view. T2*-weighted imaging showed hypointense foci in the pons, the basal ganglia, and the thalamus.*

Statistical Analyses

Multiple logistic regression analysis was performed to identify an independent risk factor of multiple L or D/I MBs. All significance levels were set at .05. Data were analyzed by PASW Statistics 18.0 (IBM, Chicago, IL).

Results

Demographic Data in AD Patients

A total of 559 patients (238 men and 321 women) participated in the present study. Mean age (standard deviation [SD]) was 78.4 (7.7) years, 78.3 (8.1) years in men and 78.6 (7.5) years in women. Clinicoradiological data are listed in Table 1. Baseline mean (SD) of MMSE was 20.2 (4.1) points. MMSE decline after 1 year had the mean (SD) of 4.2 (4.5). On CVD risk factors, current smoking was found in 61 patients (11%), hypertension in 201 (36%), diabetes mellitus in 56 (10%), dyslipidemia in 28 (5%), antiplatelet medication in 84 (15%), and anticoagulant medication in 45 (8%). Prior history of cerebral hemorrhage was found in 5 patients (1%). The mean (SD) of WMH score was 5.3 (4.0) points.

Prevalence of Cerebral MBs

Prevalence and topography of cerebral MBs are listed in Table 2. A total of 133 patients (55 men and 78 women) had at least 1 MB. Total prevalence of MBs was 24%, 23 in men and 25 in women. L MBs (≥1) were found in 71 patients (21 men and 50 women). D/I MBs (≥1) existed in 62 patients (34 men and 28 women). The topographic ratio of L and D/I MBs were 1.1, .6 in men and 1.8 in women. A total of multiple MBs were detected in 93 patients (17%), 38 (16%) men and 55 (17%) in women. Multiple L MBs existed in 49 patients (9%), 15 men (6%) and 34 women (11%). Multiple D/I MBs were present in 44 patients (8%), 23 men (10%) and 21 women (7%).

Clinicoradiological Profile of Multiple L and D/I MBs

Multiple logistic regression analysis showed that multiple L MBs were significantly associated with faster progression of dementia (Odds ratio [OR], 6.2; 95% confidence interval [CI], 1.866-20.833), development of cerebral hemorrhage (OR, 12.987; 95% CI, 3.546-17.619), and increased number of MBs (OR, 2.113; 95% CI, 1.330-4.087). A significant association was found between hypertension (OR, 19.23; 95% CI, 3.623-20.114), WMH score (OR, 3.387; 95% CI, 1.685-5.849), and multiple D/I MBs. Multiple L and D/I MBs were not linked to age, sex, smoking, dyslipidemia, diabetes mellitus, and use of antiplatelet and anticoagulant agents (Table 3, Table 4).

Table 1. *Demographic data in AD patients*

Clinical and radiological findings at baseline	
Total (men/women)	559 (238/321)
Age, mean (SD), y	78.4 (7.7)
Men	78.3 (8.1)
Women	78.6 (7.5)
MMSE, mean (SD)	20.2 (4.1)
MMSE decline after 1 y, mean (SD)	4.2 (4.5)
Current smoking, n (%)	61 (11)
Hypertension, n (%)	201 (36)
Diabetes mellitus, n (%)	56 (10)
Dyslipidemia, n (%)	28 (5)
Antiplatelet medication, n (%)	84 (15)
Anticoagulant medication, n (%)	45 (8)
WMH score, mean (SD)	5.3 (4.0)
Prior history of cerebral hemorrhage, n (%)	5 (1)

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination; SD, standard deviation; WMH, white matter hyperintensity.

Table 2. *Prevalence and topography of cerebral MBs*

Prevalence of cerebral MBs	
Prevalence of MBs ≥ 1, n (%)	
Total	132 (24)
Men	55 (23)
Women	78 (25)
Prevalence of L MBs ≥ 1, n (%)	
Total	71 (13)
Men	21 (9)
Women	50 (16)
Prevalence of D/I MBs ≥ 1, n (%)	
Total	62 (11)
Men	34 (14)
Women	28 (9)
Prevalence of multiple MBs ≥ 8, n (%)	
Total	93 (17)
Men	38 (16)
Women	55 (17)
Prevalence of multiple L MBs, n (%)	
Total	49 (9)
Men	15 (6)
Women	34 (11)
Prevalence of multiple D/I MBs, n (%)	
Total	44 (8)
Men	23 (10)
Women	21 (7)

Abbreviations: D/I, deep/infratentorial; L, lobar; MBs, microbleeds.

Discussion

The present study reported that the prevalence of MBs greater than or equal to 1 was 24% in AD patients. The prevalence of multiple MBs greater than or equal to 8 was 17%, 9% in the L topography, and 8% in the D/I topography. Multiple L MBs were associated with faster decline of MMSE score, increased number of MBs, and development of cerebral hemorrhage. Hypertension and WMH score were linked to multiple D/I MBs.

In general, the occurrence of MBs seems to increase with age in the general elderly population and can contribute to hypertension,[13,20] ischemic and hemorrhagic stroke, white matter lesions, and cognitive disorders.[6,10,21-23]

With respect to age-related MBs, MBs were significantly associated with age and male sex on a large community cohort study in Iceland.[24] The previous Dutch population-based Rotterdam Scan Study was performed in 1062 persons (mean age, 69.6 years).[13] Overall prevalence of cerebral MBs was increased with age from 17.8% at 60-69 years to 38.3% at older than 80 years on 1.5-T MRI. The prevalence of MBs was reported as 17%-32% in AD patients. There were no significant linkages between MBs and cognitive dysfunction.[6,12,15-17,25] In those studies, only 1 or a few MBs were present in most of the AD patients. A few MBs might have no clinical implications, including dementia and CVD risk factor in AD patients. The present study indicated that multiple L and D/I MBs contributed to clinicoradiological profile of AD patients.

Table 3. *Multiple logistic regression analysis of clinicoradiological factors for multiple MBs in the lobar region*

Factors	OR	95% CI	*P* value
Age	1.019	.976-1.064	.3875
Male sex	.981	.372-15.625	.3567
Smoking	1.429	.475-4.292	.5254
Hypertension	2.247	.670-7.519	.1898
Dyslipidemia	1.019	.986-1.064	.3011
Diabetes mellitus	1.701	.413-7.003	.4615
MMSE decline ≥6/y	6.211	1.866-20.833	.005
Antiplatelet use	1.587	05852-6.949	.5469
Anticoagulant use	1.099	.367-3.289	.8663
Increased MBs/y	2.113	1.330-4.087	.005
White matter lesions	1.587	.5852-6.949	.5469
Cerebral bleeding	12.987	3.546-17.619	.001

Abbreviations: CI, confidence interval; MBs, microbleeds; MMSE, Mini-Mental State Examination; OR, odds ratio.

Recent consensus of cerebral MB emphasizes that MBs can generate from 2 pathways of CAA and cerebrovascular pathology in AD patients. As the amyloid route, MBs in the corticosubcortical region might result from the deposition of amyloid β protein within the walls of blood vessels. L MBs supports CAA as the underlying vasculopathy of AD patients.[7,12-15,25] Cerebral MBs are considered as a crucial underlying process in AD because MB formation is a candidate to bridge the amyloid cascade and the vascular hypothesis. Otherwise, a strong association between cerebral MBs and hypertensive vasculopathy

Table 4. *Multiple logistic regression analysis of clinicoradiological factors for multiple MBs in the deep and the infratentorial region*

Factors	OR	95% CI	*P* value
Age	1.110	.985-1.111	.4075
Male sex	1.404	.372-11.625	.5067
Smoking	1.529	.475-5.292	.5200
Hypertension	19.23	3.623-20.114	.001
Dyslipidemia	1.501	.986-2.166	.3918
Diabetes mellitus	2.761	.413-11.011	.3617
MMSE decline ≥6/y	2.104	.372-11.655	.4568
Antiplatelet use	2.487	.665-10.909	.3667
Anticoagulant use	2.109	.467-3.689	.7688
Increased MBs/y	1.017	.531-2.117	.5876
WMH scale	3.387	1.685-5.849	.001
Cerebral hemorrhage	1.247	.870-9.519	.7898

Abbreviations: CI, confidence interval; MBs, microbleeds; MMSE, Mini-Mental State Examination; OR, odds ratio; WMH, white matter hyperintensity.

was suggested in elderly people and patients with stroke and AD. As another vascular route, D/I MBs have been correlated with CVD risk factors. Hypertensive or atherosclerotic microangiopathy can play an important role in the pathogenesis of D/I MBs. [3,4,7,13,26-28] At the same time, MBs are recognized as a surrogate marker of CAA.[28-30] Therefore, cerebral MBs could act as the common downstream product of both amyloid and vascular pathways, leading to subsequent neuronal degeneration. The present study also suggested the similar features of CAA in patients with multiple L MBs and cerebral atherosclerosis in patients multiple D/I MBs.

In addition to these 2 etiologies of MBs, how antiplatelet and anticoagulant agents can influence the generation of MBs remains unknown in AD patients. A recent longitudinal study has shown that the frequency of new MBs was increased in warfarin-treated patients with ischemic stroke during follow-up of 2 years. [31] Other studies reported previously that warfarin treatment had no significant effects on MBs frequency. [32,33] Rotterdam Scan study described that antiplatelet medication increased significantly the presence of MBs in nondemented population of more than 60 years of age.[32] Recent Japanese studies have exhibited that antiplatelet agents did not increase the prevalence of MBs in stroke patients.[33-35] Previous clinical studies revealed that several AD patients treated with aspirin had intracranial hemorrhage whereas none with placebo developed intracranial hemorrhage.[36,37] However, whether anticoagulant or antiplatelet medication increases new MBs in AD patients remains unknown currently. In the present study, both agents were not associated with multiple MBs and did not influence development of new MBs for 1 year. Little is known about incidence of cerebral MBs by prospective cohort study. Among 254 patients visiting a Dutch memory clinic, the incidence of MBs was 12% during 2 years. Apolipoprotein E genotype, the presence and progression of small vessel disease, and CVD risk factors could predict new MBs.[9] In the present study, the number of MBs was increased at 1-year follow-up in AD patients with multiple L MB. There were no significant changes in AD patients with multiple D/I MBs. The limitation of the present study was the follow-up duration of 1 year, relative small number of patients with multiple MBs, and no data of apolipoprotein E.

In conclusion, the present study indicated that the prevalence of multiple MBs was 17% in Japanese AD patients. The clinicoradiological profile suggested severe degree of CAA in patients with multiple L MB (9%) and hypertensive changes in patients with multiple D/I MBs (8%). Faster progression of dementia, development of cerebral hemorrhage, and new MBs were found in patients with multiple L MB. Hypertension and aged changes of WMH were the clinical significance in patients with multiple D/I MBs. Thus, T2*-weighted imaging is a useful tool for detecting severe degree of CAA and hypertensive vascular changes in AD patients and also give us beneficial information about further management and care in AD patients with multiple MBs.

Acknowledgments: We would like to thank Professor Yasuo Iwasaki, Department of Neurology, Toho University Omori Medical Center for the critical suggestion and support in this study.

References

1. McKhann G, Drachman D, Folstein M, et al. 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.
2. Attems J. Sporadic cerebral amyloid angiopathy: pathology, clinical implications, and possible pathomechanisms. Acta Neuropathol 2005;110:345-359.
3. Fazekas F, Kleinert R, Roob G, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol 1999;20:637-642.
4. Tanaka A, Ueno Y, Nakayama Y, et al. Small chronic hemorrhages and ischemic lesions in association with spontaneous intracerebral hematomas. Stroke 1999;30:1637-1642.
5. Kwa VI, Franke CL, Verbeeten B Jr, et al. Silent intracerebral microhemorrhages in patients with ischemic stroke. Amsterdam Vascular Medicine Group. Ann Neurol 1998;44:372-377.
6. Hanyu H, Tanaka Y, Shimizu S, et al. Cerebral microbleeds in Alzheimer's disease. J Neurol 2003;250:1496-1497.
7. Cordonnier C, van der Flier WM. Brain microbleeds and Alzheimer's disease: innocent observation or key player? Brain 2011;134:335-344.
8. Goos JD, Kester MI, Barkhof F, et al. Patients with Alzheimer disease with multiple microbleeds: relation with cerebrospinal fluid biomarkers and cognition. Stroke 2009;40:3455-3460.
9. Goos JD, Henneman WJ, Sluimer JD, et al. Incidence of cerebral microbleeds: a longitudinal study in a memory clinic population. Neurology 2010;74:1954-1960.
10. Won SS, Hwa LB, Kim EJ, et al. Clinical significance of microbleeds in subcortical vascular dementia. Stroke 2007;38:1949-1951.
11. Yakushiji Y, Noguchi T, Hara M, et al. Distributional impact of brain microbleeds on global cognitive function in adults without neurological disorder. Stroke 2012;43:1800-1805.
12. Pettersen JA, Sathiyamoorthy G, Gao FQ, et al. Microbleed topography, leukoaraiosis, and cognition in probable Alzheimer disease from the Sunnybrook dementia study. Arch Neurol 2008;65:790-795.
13. Vernooij MW, van der LA, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. Neurology 2008;70:1208-1214.
14. Lee SH, Kim SM, Kim N, et al. Cortico-subcortical distribution of microbleeds is different between hypertension and cerebral amyloid angiopathy. J Neurol Sci 2007;258:111-114.
15. Nakata-Kudo Y, Mizuno T, Yamada K, et al. Microbleeds in Alzheimer disease are more related to cerebral amyloid angiopathy than cerebrovascular disease. Dement Geriatr Cogn Disord 2006;22:8-14.

16. Cordonnier C, van der Flier WM, Sluimer JD, et al. Prevalence and severity of microbleeds in a memory clinic setting. Neurology 2006;66:1356-1360.
17. Nakata Y, Shiga K, Yoshikawa K, et al. Subclinical brain hemorrhages in Alzheimer's disease: evaluation by magnetic resonance T2*-weighted images. Ann N Y Acad Sci 2002;977:169-172.
18. Yakushiji Y, Yokota C, Yamada N, et al. Clinical characteristics by topographical distribution of brain microbleeds, with a particular emphasis on diffuse microbleeds. J Stroke Cerebrovasc Dis 2011;20:214-221.
19. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32:1318-1322.
20. Cordonnier C, Al-Shahi SR, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain 2007; 130:1988-2003.
21. Greenberg SM, Eng JA, Ning M, et al. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke 2004;35:1415-1420.
22. Werring DJ, Frazer DW, Coward LJ, et al. Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. Brain 2004;127:2265-2275.
23. Yakushiji Y, Nishiyama M, Yakushiji S, et al. Brain microbleeds and global cognitive function in adults without neurological disorder. Stroke 2008;39:3323-3328.
24. Sveinbjornsdottir S, Sigurdsson S, Aspelund T, et al. Cerebral microbleeds in the population based AGES-Reykjavik study: prevalence and location. J Neurol Neurosurg Psychiatry 2008;79:1002-1006.
25. Atri A, Locascio JJ, Lin JM, et al. Prevalence and effects of lobar microhemorrhages in early-stage dementia. Neurodegener Dis 2005;2:305-312.
26. Tatsumi S, Shinohara M, Yamamoto T. Direct comparison of histology of microbleeds with postmortem MR images: a case report. Cerebrovasc Dis 2008;26:142-146.
27. van Es AC, van der Grond J, de Craen AJ, et al. Risk factors for cerebral microbleeds in the elderly. Cerebrovasc Dis 2008;26:397-403.
28. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 2009;8:165-174.
29. Cullen KM, Kocsi Z, Stone J. Microvascular pathology in the aging human brain: evidence that senile plaques are sites of microhaemorrhages. Neurobiol Aging 2006; 27:1786-1796.
30. Schrag M, McAuley G, Pomakian J, et al. Correlation of hypointensities in susceptibility-weighted images to tissue histology in dementia patients with cerebral amyloid angiopathy: a postmortem MRI study. Acta Neuropathologica 2010;119:291-302.
31. Orken DN, Uysal E, Timer E, et al. New cerebral microbleeds in ischemic stroke patients on warfarin treatment: two-year follow-up. Clin Neurol Neurosurg 2013;115: 1682-1685.
32. Vernooij MW, Haag MD, van der Lugt A, et al. Use of antithrombotic drugs and the presence of cerebral microbleeds: the Rotterdam Scan Study. Arch Neurol 2009; 66:714-720.
33. Imaizumi T, Inamura S, Kohama I, et al. Antithrombotic drug uses and deep intracerebral hemorrhages in stroke patients with deep cerebral microbleeds. J Stroke Cerebrovasc Dis 2013;22:869-875.
34. Nishikawa T, Ueda T, Kajiwara M, et al. Cerebral microbleeds in patients with intracerebral hemorrhage are associated with previous cerebrovascular diseases and white matter hyperintensity, but not with regular use of antiplatelet agents. Neurol Med Chir (Tokyo) 2009; 49:333-339.
35. Imaizumi T, Inamura S, Kohama I, et al. Nascent deep microbleeds and stroke recurrences. J Stroke Cerebrovasc Dis 2014;23:520-528.
36. Bentham P, Gray R, Sellwood E, et al. Aspirin in Alzheimer's disease (AD2000): a randomised open-label trial. Lancet Neurol 2008;7:41-49.
37. Richard E, Kuiper R, Dijkgraaf MG, et al. Vascular care in patients with Alzheimer's disease with cerebrovascular lesions-a randomized clinical trial. J Am Geriatr Soc 2009;57:797-805.