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タイトル	Prevalence and clinicoradiological analyses of patients with Alzheimer disease coexisting multiple microbleeds.
別タイトル	多発性脳微小出血を有するアルツハイマー病患者の臨床 放射線学的特徴
作成者(著者)	長澤, 潤平
公開者	東邦大学
発行日	2017.03.28
掲載情報	東邦大学大学院医学研究科 博士論文. 63.
資料種別	学位論文
内容記述	主査: 藤岡俊樹 / タイトル: Prevalence and clinicoradiological analyses of patients with Alzheimer disease coexisting multiple microbleeds. / 著者: Junpei Nagasawa, Tetsuhito Kiyozuka, Ken Ikeda / 掲載誌: Journal of Stroke and Cerebrovascular Diseases / 巻号・発行年等: 23(9):2444 9,2014 / 本文ファイル: 出版者版
著者版フラグ	ETD
報告番号	32661 甲第852号
学位記番号	甲第578号
学位授与年月日	2017.03.28
学位授与機関	東邦大学
DOI	info:doi/10.1016/j.jstrokecerebrovasdis.2014.05.036
その他資源識別子	https://www.sciencedirect.com/science/article/pii/S1052305714002833?via%3Dihub
メタデータのURL	https://mylibrary.toho.u.ac.jp/webopac/TD77506375

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

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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 \geq 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.

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

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<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 \times 230 mm; matrix 256 \times 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

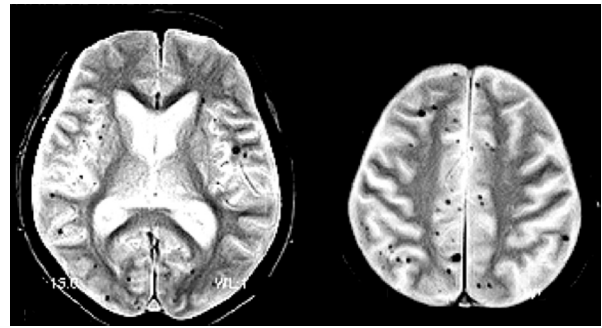


Figure 1. Multiple lobar microbleeds. T2*-weighted imaging showed round-shaped hypointense foci in the cerebral cortex and the subcortical region.

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.

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 \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg) or currently under treatment; diabetes mellitus (fasting blood sugar \geq 126 mg/dL or hemoglobin A_{1c} \geq 6.5%) or currently under treatment; dyslipidemia (serum low-density lipoprotein cholesterol \geq 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.

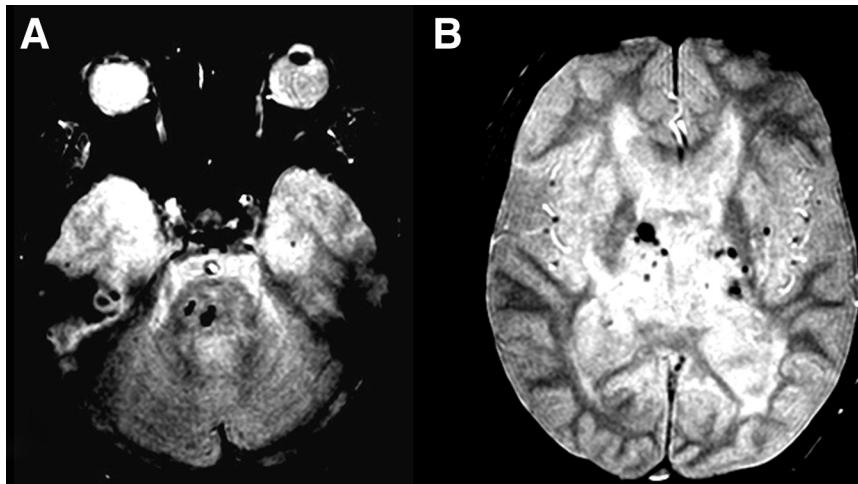


Figure 2. Multiple deep and infratentorial microbleeds. (A) Infratentorial view. (B) Deep regional view. T2*-weighted imaging showed hypointense foci in the pons, the basal ganglia, and the thalamus.

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

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	0.5852-6.949	.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.

AD patients. The present study indicated that multiple L and D/I MBs contributed to clinicoradiological profile of AD patients.

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.

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