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 312 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 132 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.

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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.

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.

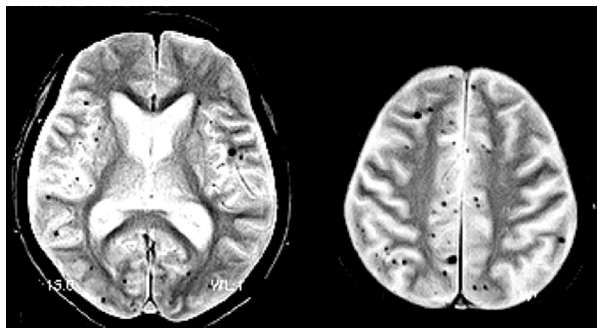

Figure 1. *Multiple lobar microbleeds. T2*-weighted imaging showed round-shaped hypointense foci in the cerebral cortex and the subcortical region.*

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.