Original Article

The clinical significance of brain microbleeds in patients with Alzheimer's disease: Preliminary study

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Abstract

Background: Microbleeds (MBs) are observed frequently in Alzheimer's disease (AD) and suggested to play a crucial role in the pathophysiology, but their clinical significance remains unclear. **Materials and Methods:** The study recruited 100 patients with AD who were diagnosed at the memory clinic in Seoul Medical Center in 2014. For each patient, baseline characteristics, neuropsychological tests, cerebrovascular risk factors, medial temporal lobe atrophy (MTLA), and severity of small vessel disease (SVD) according to the existence of MBs were evaluated. **Results:** The prevalence of MBs in patients with AD was 33%. The percentage of male gender, the severity of SVD and MTLA were significantly increased in MB(+) group. The MB(+) group showed more severe MTLA and SVD than MB(−) group. **Conclusions:** These results suggested that MBs might reflect the burden of amyloid and ischemic vascular pathology.

Key Words

Alzheimer disease, cognition, microbleeds

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Ann Indian Acad Neurol 2016;19:495-498

Introduction

According to the previous trial, microbleeds (MBs) were common in Alzheimer's disease (AD) with a prevalence rate of 23%. Especially, it was higher than normal cognitive function or mild cognitive dysfunction group.[1] Further, in a study using Pittsburgh compound B (PiB) positron emission tomography, the amyloid accumulated a lot in MB area, indicating that the MB reflected an amyloid burden that is regarded as pathophysiology of AD.[2]

However, the clinical implication of MBs was not clearly defined. Although there are some debates, several studies failed to reveal the influence of MBs on cognitive function.[3,4] Moreover, there are no recommendations or guidelines to manage the AD patients with brain MBs.[5] Clinicopathologic factors that correlated with MBs in patients with AD remain unclear.[5] Considering no cure for AD, the need for making diverse strategies to manage AD is increasing. Thus, we investigated the relationship between MB and clinical manifestation, cognitive function, small vessel disease (SVD), and medial temporal lobe atrophy (MTLA) in AD patients.

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.194426

Materials and Methods

Patients

The study recruited consecutively 100 patients who were over age 60 and diagnosed as AD after proceeding brain magnetic resonance imaging (MRI) including Gradient echo image, at Seoul Medical Center Memory clinic from September 2014 by two neurologist (J.H.H and J.Y.A). The Institutional Review Board of Seoul Medical Center approved the study, and all subjects provided written informed consent to participation.

How to cite this article: Heo JH, Im DG, Lee SH, Ahn JY. The clinical significance of brain microbleeds in patients with Alzheimer's disease: Preliminary study. Ann Indian Acad Neurol 2016;19:495-8.
Received: 14-03-16, **Revised:** 28-04-16, **Accepted:** 29-07-16

The clinical manifestation such as age, gender, education, cerebral infarction history, hypertension, diabetes, hyperlipidemia, cardiac disease, smoking, and antiplatelet usage was investigated. For thorough cognitive examination, we used Seoul Neuropsychological Screening Battery as an investigation tool.[6] In short, it consisted of Korean version of mini–mental state examination (MMSE), attention tests (digit span, letter cancellation), language and related function tests (spontaneous speech, comprehension, repetition, Korean-Boston Naming Test, reading, writing, finger naming, right-left identification, calculation, praxis), visuospatial function test (Rey Complex Figure Test), memory tests (Seoul Verbal Learning Test, Rey Complex Figure Test), Frontal/Executive function tests (Controlled Oral Word Association Test, Korea-Color Word Stroop Test), Geriatric Depression Scale, daily function test (Barthel Activities of Daily Living), and clinical dementia rating (CDR) scale. Diagnosis of AD was made if the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria for probable AD was satisfied.[7] Patients were excluded if they had any other neurodegenerative disorders or cognitive impairments resulting from brain tumor, trauma, hypoxic injury, infection, metabolic disease, mental retardation, epilepsy, stroke, and other psychotic disease.

Brain image analysis

The 3.0T MRI (Achieva 3.0 TX, Philips) was applied for all study with 5 mm thickening transverse plane, using T2-weighted, T2-weighted gradient echo image, T1-weighted, fluid-attenuated inversion recovery (FLAIR) image. For each image, time to echo and time to repeat were as follows; 80 ms and 3000 ms in T2-weighted image, 16 ms and 460 ms in T2-weighted gradient echo image, 10 ms and 550 ms in T1-weighted image, 125 ms and 8000 ms in FLAIR image. MB was defined as a round or oval shaped lesion of which more than half was surrounded with parenchyma and presenting low signal in T2-weighted gradient echo image and not high signal in T1- and T2-weighted image.[8] Low signal lesions symmetrically in basal ganglia were regarded as calcification or iron accumulation.[9] MRI evaluation was performed independently by two neurologists (J.H.H. and D.G.I.). In cases of discordance, the scores were determined by discussion.

SVD was defined as a lesion presenting high signal in T2 and FLAIR without definite low signal in T1. Fazekas scale was used for severity classification.[10] The severity was classified into four grades, ranging from Grade 0 with no SVD to Grade 3 with severe SVD. When comparing SVD grade of the subcortical area and periventricular area, we used more severe one as final severity score of the patient.[11]

A visual scale using axial image was used for measuring degree of MTLA, as it already presented high similarity with Schelten's visual scale using coronal image.[12] The atrophy severity was classified as five grades in T1-weighted image, ranged from Grade 0 with no atrophy to Grade 4 with severe atrophy. The score of the MTLA was obtained by summing the left and right scores.

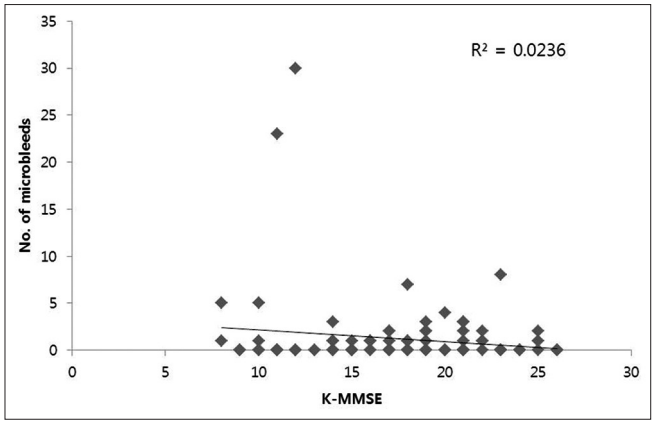

Figure 1: Correlation between mini–mental state examination and Microbleeds in Alzheimer's disease patients

Statistical analysis

Student's *t*-test and Chi-square test were used for intergroup comparisons of continuous values and categorical variables, respectively. The correlations of number of MBs with the MMSE score were analyzed by bivariate correlation analysis. All data were presented as mean ± standard deviation (SD) values, and the required two-tailed level of significance was set at 0.05.

Results

The patients' clinical manifestation was summarized in Table 1. Totally 100 AD patients were enrolled. Mean age of the patients was 78.07 (SD 6.97), and 42 patients were male. Regarding neuropsychiatric examination, mean score for MMSE and CDR was 17.42 (SD 4.83) and 1.14 (SD 0.63), respectively. When investigating the risk factors of cerebrovascular disease, the patients had past medical histories as follows; stroke (17 patients),

Table 1: Baseline characteristics of the 100 patients with Alzheimer's disease

Variables	AD (*n*=100)
Sex, *n* (%)	
Male	42
Female	58
Age (year)	
Mean±SD	78.07±6.97
Education (year)	
Mean±SD	5.98±5.39
MMSE	17.42±4.83
CDR	1.14±0.63
Stroke, *n*	17
HTN, *n*	63
Diabetes, *n*	30
Hyperlipidemia, *n*	47
Heart disease, *n*	22
Smoking, *n*	11
Antiplatelet medication, *n*	45
Anticoagulation medication, *n*	3
SVD (grade)	1.37±0.91
MTLA (grade)	4.55±1.87
MBs, *n*	33

SD = Standard deviation, MMSE = Mini-mental state examination, CDR = Clinical dementia rating, SVD = Small vessel disease, MTLA = Medial temporal lobe atrophy, MBs = Microbleeds, HTN = Hypertension, AD = Alzheimer's disease

hypertension (63 patients), diabetes (30 patients), hyperlipidemia (47 patients), cardiac disease (22 patients), and smoking (11 patients). Totally 45 patients had been treated with an antiplatelet agent and 3 patients with an anticoagulant.

The average degree for SVD and MTLA were 1.37 and 4.55, respectively. In total, 123 MBs were found in the study population, and among them, 22 MBs were found in the basal ganglia/thalamus, 23 MBs were in the infratentorial area such as cerebellum and brainstem, and 78 MBs were in the frontal, temporal, parietal, and occipital area [Table 2].

The patients were divided into two groups as MB(+) and MB(−). There were significant differences in gender ($P = 0.0268$), SVD grade ($P = 0.0004$), and MTLA severity ($P = 0.0123$) between groups [Table 3]. There were more male patients in MB(+) group. Furthermore, SVD and MLTA were more severe in MB(+) group.

Table 2: Number and location of microbleeds in patients with Alzheimer's disease

Location	Number of MBs
Basal ganglia/thalamus	22
Infratentorial	23
Lobar	
Frontal	19
Temporal	17
Parietal	30
Occipital	12
Total	123

MBs = Microbleeds

Table 3: Comparison between microbleed positive and microbleed negative patients with Alzheimer's disease

Location	AD		*P*
	MB(+) (*n*=33)	MB(-) (*n*=67)	
Sex			
Male, *n* (%)	19	23	0.0268
Age	77.42±6.04	78.39±7.40	0.5181
Education	7.17±5.6	5.40±5.22	0.1226
Risk factors			
Stroke	6	11	0.8252
HTN	22	41	0.7545
DM	9	21	0.8527
Hyperlipidemia	11	36	0.0875
Heart disease	5	17	0.3662
Smoking	4	7	0.8014
Antiplatelet	14	31	0.8811
Anticoagulation	1	2	0.9901
MMSE	17.33±4.61	17.46±4.97	0.9006
CDR	1.19±0.69	1.11±0.59	0.5859
SVD	1.82±0.81	1.15±0.88	0.0004
MTLA	5.21±1.50	4.22±1.96	0.0123

Data represent the mean±SD. HTN = Hypertension, DM = Diabetes mellitus, MMSE = Mini-mental state examination, CDR = Clinical dementia rating, SVD = Small vessel disease, MTLA = Medial temporal lobe atrophy, SD = Standard deviation, MB = Microbleed, AD = Alzheimer's disease

There was no significant correlation between MMSE and the number of MBs (Pearson's correlation coefficient = −0.1537, $P = 0.1268$) [Figure 1]. The correlation with the number of MBs was only found in SVD ($P = 0.023$, $R^2 = 0.053$, linear regression analysis). The existence of MB was affected by two variables, i.e., gender ($P = 0.007$) and SVD ($P = 0.001$) on binary regression analytic method.

Discussion

In this study, MB was found in 33% of total AD patients. It was higher than the prevalence in subjects with normal cognitive function in the previous study (0–19%) and also relevant with AD patient group (18–32%).[13] MB was generally distributed in cerebrum, basal ganglia, and infratentorial area. Previous studies consistently reported that MBs presented lobar distribution mainly.[14,15] In this study, 63% of MBs were located in lobes despite its general distribution, so that the result was consistent with other studies.

In this study, the SVD severity was most correlated with the number of MBs. Some longitudinal observational studies reported that new MBs were related with the previous one.[16-18] These results together with the findings of this study support that underlying SVD affects the MB. MB is receiving attention as a risk factor for cerebral hemorrhage and cognitive dysfunction. Most cross-sectional studies reported that MBs worsened the executive function, attention, processing speed, and global cognition, although the results were not consistent.[19-21] Few studies reported the relationship between MB and cognitive function in AD patients. However, according to Pettersen *et al*., AD patients with MB presented more severe SVD than patients without MB; also, there was no relation between MB and cognitive function, corroborating our findings.[4]

MBs are also regarded as manifestation of SVD commonly found in MRI, such as white matter hyperintensities and lacunar infarction. According to Seo *et al*., in subcortical vascular dementia patients, MBs were related with cognitive impairment in various areas even after controlling age, education, ischemic changed, and lacune.[22] They suggest that MBs, as well as ischemia, could be an important pathomechanism of cognitive dysfunction. However, clinical implication of MB in subcortical vascular dementia and MB in AD seems to differ. Although MBs in AD patients were related with SVD severity, MBs would be originated from cerebral amyloid angiopathy (CAA) rather than general ischemic factor such as hypertension.[3,23] Furthermore, the autopsy of AD patients mostly presented some pathologic findings of CAA regardless of severity, which suggested that the underlying CAA affects MBs in AD patients.[24]

MBs are regarded as a candidate for connecting amyloid cascade hypothesis and vascular hypothesis, which are main two hypothesis for AD pathogenesis.[1] AD patients with more than 8 MBs presented lower level of amyloid-beta 1–42 in cerebrospinal fluid, as compared to AD patients without MBs,[25] implicating the relationship between amyloid burden and MBs. Although the significance of MTLA disappeared after regression analysis in this study, there was more severe MTLA

in MB(+) group. Further investigations of the relationship between MBs and AD pathology are needed.

In MB(+) group, the MLTA were more severe than those of MB(−) group. Previously, many pathologic studies revealed that MTLA is associated with neurofibrillary tangle (NFT) pathology.[26] In this study, the MMSE were not different between the groups despite severe MTLA in MB(+) group, which means that factors other than currently known neuropathologic changes such as NFT or amyloid plaques could affect the cognitive function.

This study has several limitations. First, the AD patients were not confirmed pathologically. Second, there was no information of pathologic severity of underlying CAA. Third, the correlation between cognitive domains and MBs location was not analyzed in depth. Fourth, it was a preliminary study without a normal control group. Thus, further investigation into the clinical implication of MBs in AD patients would be needed.

Financial support and sponsorship
This study was supported by grants of the Samjin Pharmaceuticals Co. Ltd.

Conflicts of interest
There are no conflicts of interest.

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