Original Article

Effects of Microbleeds on Hemorrhage Development in Leukoaraiosis Patients

Seung-Hoon LEE, Jae-Hyeok HEO, and Byung-Woo YOON

The possible influences of cerebral microbleeds (CMBs) on the development of intracerebral hemorrhage (ICH) in patients with leukoaraiosis (LA) have rarely been examined. We aimed to determine whether CMBs might be a risk factor for ICH in hypertensive patients with leukoaraiosis. We studied 70 hypertensive patients with acute ICH and LA (the ICH group) by brain MRI, including T_2*-weighted gradient-echo sequences. The control group was composed of 73 hypertensive LA patients without ICH. CMBs and old lacunae were counted in the group of patients with ICH and in the control subjects and compared. The ICH group contained more patients with CMBs (68 patients; control group, 41; $p<0.01$), and showed a higher mean number of lesions (19.9±31.1; control group, 7.4±19.6; $p<0.01$). The negative predictive value for ICH was highest among the ICH patients without CMB (94.1%), and the positive predictive value was highest among the ICH patients with 6 or more CMBs (75.4%). Old lacunae were observed more frequently in the ICH group (65 patients; control group, 58; $p=0.02$), but their predictive value for ICH was not high (positive, 52.3%; negative, 75.0%). Our results indicated that CMBs may be used to predict the risk of ICH in hypertensive patients with advanced LA. (*Hypertens Res* 2005; 28: 895–899)

***Key Words*: magnetic resonance imaging, hypertension, intracerebral hemorrhage, lacunar infarction**

Introduction

Leukoaraiosis (LA) refers to bilateral and either patchy or diffuse areas of hyperintensity on T_2-weighted MRI or fluid-attenuated inversion recovery MRI associated with hypertension (*1*) or smoking (*2*). Although the causal relationship between LA and intracerebral hemorrhage (ICH) remains uncertain, it is evident that LA is more prevalent among patients with ICH than among those without ICH (*3*, *4*). Recently, it has been reported that cerebral microbleeds (CMBs) observed on T_2*-weighted gradient-echo MRI are closely associated with the presence of ICH (*5*, *6*). CMBs are observed by pathological examination as tiny old bleedings that resulted from the rupture of lipohyalinized arterioles (*7*), and have been shown to be well correlated with increasing LA grade (*8*). However, the possible influences of CMBs on the development of ICHs in patients with LA have rarely been examined. Because there is no specific treatment for ICH as compared with that for ischemic stroke, and also because the incidence of ICH is relatively high in Asia, it is extremely important that asymptomatic cerebral lesions be discovered in order to enable the prediction of future ICH events. In this case-control study, we assessed the predictive value of CMBs for ICH in hypertensive patients with LA, and we compared the predictive value of CMBs in these patients with that of silent lacunae.

Methods

The data were obtained in the setting of a single-center, hospital-based study from January 2002 to September 2003. Sev-

From the Department of Neurology, Seoul National University, Seoul, Republic of Korea; and Neuroscience Research Institute, Clinical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea.

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Address for Reprints: Byung-Woo Yoon, M.D., Department of Neurology, Seoul National University Hospital, 28 Yeongeon-dong, Jongno-gu, Seoul, 110–744, Republic of Korea. E-mail: bwyoon@snu.ac.kr

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Table 1. Baseline Characteristics of the Patients

	ICH	
	Present (n=70)	Absent (n=73)
Age	69.5±10.0	70.2±9.6
Male sex	38	41
Hypertension	70	73
Systolic BP (mmHg)	162±23	158±27
Diastolic BP (mmHg)	92±15	89±13
Duration of hypertension (months)	58±7	48±65
Diabetes	18	25
Smoking*	10	23
Heart or peripheral artery disease	26	28
Prior use of antiplatelet agents	12	10
Cholesterol (mmol/l)	4.93±1.53	4.88±1.12
Hematocrit	39.8±4.8	39.5±4.9
Creatinine (μmol/l)	89.4±62.2	92.7±53.7
Glucose (mmol/l)	6.79±2.76	6.99±2.93

Pearson's χ^2 test or Student's t-test (mean±SD) was used. ICH, intracerebral hemorrhage; BP, blood pressure. *$p<0.05$.

enty unselected, consecutive, unrelated hypertensive subjects with first-ever acute ICH and LA were enrolled in the study. All patients had acute ICH, as diagnosed by CT images, and all patients presented with the clinical signs and symptoms related to the location of the hematoma. From among those who visited our clinic, we selected 73 hypertensive subjects with LA but without ICH as controls; these subjects were matched to the former group of patients according to sex and age. Hypertension was diagnosed according to previously reported criteria (*9*). LA was diagnosed according to Fazekas's criteria (*10*), according to whether a subject had one of the following 1) multiple periventricular hyperintense punctate lesions and early confluence, or 2) multiple areas reaching confluence, as seen on T_2-weighted MRIs.

MRI was performed on a 1.5 T superconducting magnet system (Signa, GE Medical Systems, Milwaukee, USA). T_2*-weighted gradient-echo MRIs were obtained in the axial plane with the following parameters: repetition time/echo time, 500/15 ms; flip angle, 26°; and matrix size, 256 × 192. Standard T_1- and T_2-weighted sequences were also obtained. CMBs were defined as small foci of signal loss on gradient-echo MRI, and these areas were located and quantified independently by two experienced neurologists on a consensus basis without knowledge of the clinical information. Inter-observer agreement was found to be very good (κ=0.87). Silent lacunae were defined as small lesions of hyperintensity on T_2-weighted MRI and corresponding distinctive low-intensity areas on T_1-weighted MRI.

Standard statistical tests in SPSS version 10.0 were used for the statistical analysis. Dichotomous variables were analyzed using the χ^2 test, and continuous variables using the Student's t-test were used for normally distributed data. The Mann-Whitney U test was used for data that was not normally distributed. The positive predictive value of the CMBs was estimated by the ratio of the number of patients who had CMBs and ICH to the number of all patients with CMBs; the negative predictive value of the CMBs was defined by the ratio of the number of patients who had neither CMBs nor ICH to the number of all patients without CMBs. Thus, a positive predictive value of CMBs indicated the possibility that the presence of such lesions could be predictive of the presence of ICH; furthermore, a negative predictive value was considered to predict the absence of ICH.

Results

The patients' backgrounds are summarized in Table 1. The number of smokers was significantly lower in the ICH group. Table 2 shows the distribution of CMBs and silent lacunae in each of the groups. CMBs were present in 68 patients (97.1%) in the ICH group and in 41 patients (56.2%) in the control group ($p<0.01$), as shown typically in Fig. 1. The mean number of lesions was significantly higher in the ICH group (Fig. 2). As regards cerebral location, the CMBs were observed more frequently in all area categories in the ICH group than they were in the control group ($p<0.01$ at all locations). The ICH group also showed a higher number of patients with silent lacunae ($p=0.02$), although the mean number of lesions was not significantly different for the two groups. To determine the clinical usefulness of the data, we analyzed the positive and negative predictive values of each variable for ICH. The negative predictive value for ICH was highest among the ICH patients without CMB, and the positive predictive value was highest among those with ICH and with 6 or more CMBs. From among the different locations observed here, CMBs in the basal ganglia were associated with the highest positive and negative predictive values for ICH.

Discussion

An association between LA and ICH has been demonstrated in several clinical studies (*3*, *4*). A hospital-based study revealed that extensive LA was more than twice as prevalent among patients with ICH than among patients without ICH (*3*). Moreover, the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) also indicated that LA was an independent predictor of all anticoagulation-related hemorrhages (hazard ratio=2.7) (*4*). Although LA is known to be frequently observed in patients with ICHs, it has also been suggested that LA is an intermediate surrogate, rather than a risk factor for ICH (*11*). This relationship may be related to the expectation that LA is a neuroimaging finding caused by several different pathological changes such as demyelination, gliosis, and small deep infarcts, and thus is caused by a variety of etiologies (*11*).

In several recent clinico-radiologic reports it has been noted that CMBs are strongly associated with the presence of ICHs

Table 2. Distribution of CMBs and Silent Lacunae

	ICH		*p* value	Predictive value (%)	
	Present (n=70)	Absent (n=73)		Positive	Negative
CMBs					
Present	68	41	<0.01	62.4	94.1
≥6 lesions	49	16	<0.01	75.4	73.1
Mean±SD	19.9±31.1	7.4±19.6	<0.01		
Distribution					
Cortico-subcortical	50	29	<0.01	63.3	68.8
Basal ganglia	54	22	<0.01	71.1	76.1
Thalamus	49	23	<0.01	69.0	70.4
Infratentorial	43	23	<0.01	65.2	64.9
Silent lacunae					
Present	65	58	0.02	52.3	75.0
Mean±SD	5.8±3.8	6.5±6.9	0.50		

ICH, intracerebral hemorrhage; CMB, cerebral microbleeds.

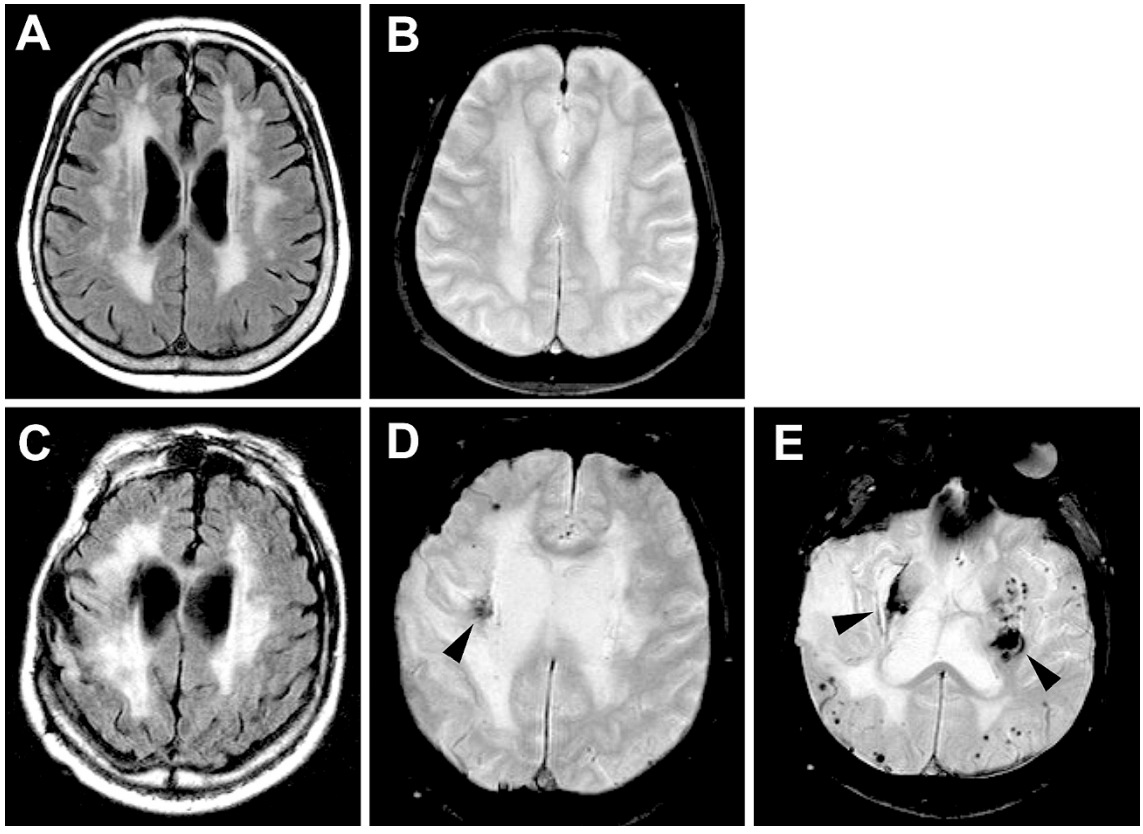

Fig. 1. *Representative slices showing an association between cerebral microbleeds (CMBs) and intracerebral hemorrhage. The data from both of the patients with hypertension shown here (a 59-year-old man [A, B] and a 76-year-old woman [C–E]) show advanced leukoaraiosis, as visualized by fluid-attenuated inversion recovery images (A and C). Numerous CMBs were observed only in the case below (D and E), which also showed two hemorrhagic lesions (arrowheads).*

(*9*, *12*). CMBs have been studied by gradient-echo MRI, which can be used to detect small calcifications or microhemorrhages *via* magnetic susceptibility effects. CMBs are usually caused by chronic hypertension (*13*), and are recognized as being well correlated with the extent of left ventricular hypertrophy (*14*). Moreover, the association with ICH was

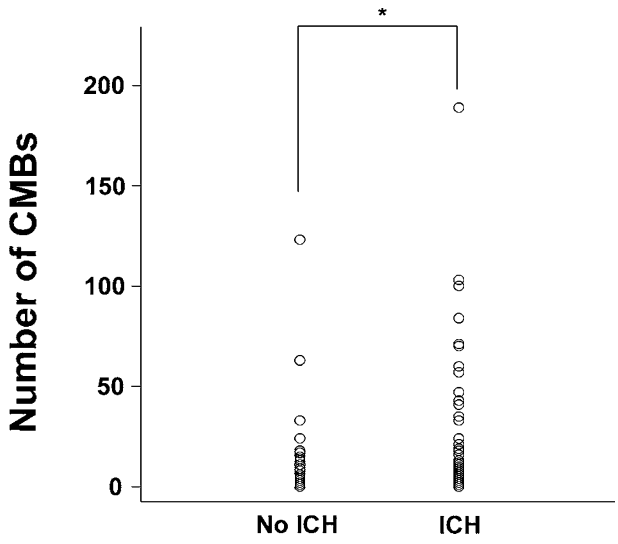

Fig. 2. *Distribution of cerebral microbleeds (CMBs). The number of CMBs was significantly higher in the ICH group than in the control group (*$p < 0.01$*).*

also very strong, the cerebral locations of the CMBs coincide with the locations of ICHs (*9*). Because the topographical distribution of CMBs differs from that of lacunar infarctions, which may represent occlusion-type microangiopathy (*8*, *15*, *16*), findings of CMB imaging should be considered suggestive of bleeding-prone microangiopathy. In this study, we aimed to predict the development of ICH more accurately by analyzing CMBs in LA patients. As a result, when we restricted the number of CMBs to ≥6 lesions, we found that the positive predictive value for ICH increased to 75.4%. As regards the locations of these CMBs, even though the differences were not very high, the predictive value was highest when they were located in the basal ganglia. Silent lacunar infarctions contributed little to the prediction of ICH. However, our study was limited by its cross-sectional nature. Because we did not prospectively analyze the occurrence of ICH by follow-up imaging, the predictive value of CMBs for ICH might not be applicable in this context. However, in view of the fact that CMBs and LA are not acute, but instead represent old lesions, as indicated by previous reports (*7*), they would have occurred before the development of ICH. This conclusion is based on the prospective observation that CMBs are risk lesions for subsequent ICHs (*17*). Another limitation of this study was the lack of the total blinding of the reader to the presence of ICH on the same image. To resolve this potential bias, the reader should not have been informed of our hypothesis at the start of the study. Because the clinical and imaging data, including the regional data, were already secured prior to the planning of this study, we did not believe that this bias unduly influenced our results.

Our results indicated that CMBs may help predict the occurrence of ICH in hypertensive patients with advanced LA. Our data suggest that the possibility of future ICHs should be considered in patients with advanced LA and also with several CMBs; such patients should be monitored carefully including reduction of the use of methods of management that could potentially increase the tendency to bleed. Before using the present findings for clinical application, our results should be confirmed by a prospective cohort study of a large population.

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