Gradient Echo Magnetic Resonance Imaging in the Prediction of Hemorrhagic vs Ischemic Stroke

A Need for the Consideration of the Extent of Leukoariosis

Dong-Eog Kim, MD; Hee-Joon Bae, MD; Seung-Hoon Lee, MD; Ho Kim, PhD; Byung-Woo Yoon, MD, PhD; Jae-Kyu Roh, MD, PhD

Background: Multifocal signal loss lesion (MSLL) on gradient echo magnetic resonance imaging (GE-MRI) may reflect bleeding-prone microangiopathy. However, MSLLs are also known to be associated with leukoariosis; leukoariosis is commonly associated with occlusive-type vascular lesions.

Objective: To determine whether MSLL on GE-MRI is significantly associated with the type of stroke—intracerebral hemorrhagic (ICH) stroke more often than an ischemic stroke (infarction)—regardless of the extent of leukoariosis.

Patients and Methods: We studied 91 patients who had an acute stroke and were admitted to the Department of Neurology, Seoul National University Hospital, Seoul, South Korea, from March 1, 1997, to July 31, 1998. These patients underwent both conventional MRI and GE-MRI. The GE-MRI was used to count MSLLs. We also counted lacunae and classified leukoariosis (none or mild and advanced). Multiple logistic regression analysis was used to test for MSLL–leukoariosis interaction association with the type of stroke (ICH over infarction) and to evaluate the relative contribution of an MSLL—adjusted for age, sex, and lacunae—in discriminating the type of stroke.

Results: The association between MSLL and ICH statistically significantly differed by leukoariosis ($P = .003$ for MSLL–leukoariosis interaction term). The MSLL count on GE-MRI was significantly associated with the type of stroke (ICH over infarction; odds ratio, 2.46; 95% confidence interval, 1.38-4.39) when leukoariosis was classified as none or mild. When leukoariosis was classified as advanced, there was a decrease in the odds ratio of MSLL to 0.99 (95% confidence interval, 0.94-1.04).

Conclusions: Our findings indicate that MSLL on GE-MRI is a predictor of ICH vs infarction in patients with no or mild leukoariosis, but not in patients with advanced leukoariosis. Therefore, in the evaluation of GE-MRI for a bleeding-prone microangiopathy, the extent of leukoariosis should be considered.

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MULTIFOCAL SIGNAL LOSS LESIONS (MSLLs) ON T2*-Weighted Gradient Echo Magnetic Resonance Imaging (GE-MRI) REPRESENT PREVIOUS MICROBLEEDINGS,1,2 WHICH MAY BE A DIRECT MARKER OF INCREASED VASCULAR FRAgilITY IN PATIENTS WITH VARIOUS TYPES OF SMALL VESSEL DISEASE.1,4 Many researchers speculate that GE-MRI might enable the recognition of bleeding-prone microangiopathy and the prediction of a patient’s hemorrhagic risk. Thus, it is also believed to be helpful in the selection of patients for different types of secondary prevention of stroke.4,6

However, the same type of small vessel disease can cause ischemic lesions or leukoariosis as well as intracerebral hemorrhages (ICH).5,7,9 Since MSLL reflects microangiopathy,1 it may be associated with leukoariosis8,10,11; the latter is commonly associated with occlusive-type vascular lesions. Therefore, in advanced leukoariosis, there is a possibility that GE-MRI might not predict a patient’s risk of ICH over an ischemic stroke (Figure 1). To confirm this, we tried to determine whether an MSLL on a GE-MRI is significantly associated with the type of stroke—ICH more than an ischemic stroke (infarction)—regardless of the extent of leukoariosis.

RESULTS

As shown in Figure 2A, the number of MSLLs and lacunae were significantly higher ($P = .00$, Mann-Whitney test) in 30 patients with advanced leukoariosis (5.0 [6.9] MSLLs and 18.5 [10.7] lacunae) than in 61 patients with no or mild leukoariosis (2.1 [2.0] MSLLs and 9.7 [3.3] lacunae). Table 1 data show that the ICH group (n=33) and the infarction group (n=58) did not differ for age, sex, and stroke risk factors including hypertension, diabetes mellilitis.
PATIENTS AND METHODS

PATIENT POPULATION

The cohort consisted of 116 consecutive patients who had an acute stroke and were admitted to the Department of Neurology, Seoul National University Hospital, from March 1, 1997, to July 31, 1998, and underwent both conventional MRI and GE-MRI. After exclusion of 25 subjects, 91 patients (58 men, 33 women; mean [SD] age, 64.3 [9.7] years; age range, 37-89 years) were included. Exclusionary criteria were (1) patients who did not have relevant imaging findings that explained the neurologic symptoms, (2) transient ischemic attack without progression to completed stroke, and (3) strokes due to miscellaneous causes such as aneurysm, vasculitis, moyamova disease, hematologic disorders, hypercoagulable states, arteriovenous malformation, and venous sinus thrombosis.

CLINICAL EVALUATION

All patients underwent systematic investigations, including complete blood cell count, blood chemistry studies, lipid profiles, coagulation abnormalities, urinalysis, chest x-ray film, electrocardiogram, computed tomographic scan (CT), MRI, and MR angiography. In selected patients, transthoracic and transesophageal echocardiography, including a microbubble contrast test, transcranial Doppler, and catheter angiography, were also performed.

MRI EVALUATION

All MRI studies were performed on a 1.5-T superconducting magnet (Signa; GE Medical Systems, Milwaukee, Wis). The standardized MRI protocol consisted of axial T2-weighted spin-echo (repetition time, 2500-4500 milliseconds; echo time, 80-112 milliseconds; flip angle, 20°; slice thickness, 5 mm; and gap width, 2 mm), axial

The following cerebrovascular risk factors were recorded for all patients: hypertension, diabetes mellitus (history of diabetes mellitus with or without current treatment or fasting blood glucose levels >140 mg/dL [>7.8 mmol/L]), smoking (current or ex-smoker who had quit smoking <5 years before admission), abnormal cholesterol levels (<160 or >239 mg/dL [<4.14 or >6.21 mmol/L]), history of stroke, and previous medications (antiplatelet agents or anticoagulants) received. Hypertension was considered to be present if a subject had 2 or more of the following conditions: (1) repeated blood pressure readings above 160/95 mm Hg at intervals of 1 week, (2) a history of hypertension and/or use of antihypertensives, (3) findings of target organ damage including hypertensive retinopathy on optical fundus examination or left ventricular hypertrophy on echocardiography or echocardiography. The potential stroke mechanisms were determined according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST).

Locations of ICH were classified as deep (thalamus and basal ganglia), lobar, or infratentorial.

There was no significant difference in the previous medications between groups that could predispose to bleeding. In the no or mild leukoariosis group, 3 of 7 patients who had used antiplatelet agents had ICH. All 3 patients with ICH also had MSLLs, but the remaining 4 patients with an infarction did not. In the advanced leukoariosis group, 2 patients had taken antiplatelet agents and they presented with ICH. One of them had MSLLs; the other did not. Only 1 patient had used warfarin sodium therapy; the patient had no or mild leukoariosis and presented with an infarction. As given in Table 3, locations for MSLLs and ICH did not differ significantly between the 2 leukoariosis groups. Although there were more lobar ICHs in the no or mild leukoariosis group (n = 6) than in the advanced leukoariosis group (n = 2), the frequencies were similar (6 of 61 patients and 2 of 30 patients, respectively). In both groups, a few patients with lobar ICH had more than 4 MSLLs with a lobar location only (n = 2 and n = 1, respectively). In the advanced leukoariosis group, most of those with large or small artery infarctions had MSLLs, which was contrary to the GE-MRI findings of absent MSLLs in those who had infarction in

Figure 1. A 69-year-old woman with hypertension had advanced leukoariosis (A) and numerous multifocal signal loss lesions (black arrow) (B); an acute ischemic lesion of internal capsule (C, white arrow) developed, which is found to overlap with the nearby multifocal signal loss lesions (black arrow, part B).
multiple lacunar stroke.17 Also, considering the close link be-
not discriminate between major hemorrhagic or mul-
bers of both lacunae and MSLLs in patients with ad-
leukoariosis group. When one considers the higher num-
advanced leukoariosis than in those patients with no or mild
leukoariosis, it is probably the case that arteriosclerotic changes related to long-standing exposure to stroke risk factors as the shared causative basis9 may have resulted in both occlusion and rupture.5,22,23 For example, the cerebral complications of patients with hypertension may vary; either rupture or occlusion of the diseased small artery may result in parenchymal hemorrhage, lacunar infarction, or widespread leukoariosis depending on the circumstances.5,7,23 In support of these, pathologic changes in ICH such as lipohyalinosis,7 microaneurysms,15 and fibrinoid degeneration21 have also been found in subjects with chronic hypertension, lacunae, and leukoariosis.9 Clinically silent ischemic lesions as well as previous hemorrhages are a common finding on the MRIs of patients with primary intracerebral hematomas.1 Prior ischemic infarction was also reported to be one of the risk factors for intracerebral hemorrhage.6,9,12 Moreover, some have argued20,27 and supported27 that ICH requires an underlying ischemic lesion to set the chain of hemorrhagic events in motion.

T2*—weighted GE sequences (repetition time, 200–500 mil-
liseconds; echo time, 15 milliseconds; flip angle, 20°; field
of view, 220×170 mm; acquisition matrix size, 256×192
pixels; number of excitations, 2; slice thickness, 1.4 mm;
and gap width, 0.7 mm). Brain CT scan and T2-weighted
MRI were used to identify leukoariosis, ICH, and infarc-
tion. Leukoariosis was classified as absent, punctate, early
confluent, or confluent abnormalities according to Fazekas
et al.13 Then, the former 2 were defined as no or mild leu-
koariosis and the latter 2 as advanced leukoariosis. This di-
ichtomization was performed on the basis of previous study
findings that showed that punctate foci cannot be attrib-
uted unequivocally to brain ischemia and more extensive
abnormalities reflect a true ischemic process.14-16 Areas of
parenchymal ischemic destruction with a diameter of less
than 10 mm were termed “lacunae” and counted. The GE-
MRI was used to count focal areas of homogenous round
signal loss with a diameter of up to 3 mm (MSLLs, Figure
1), unless CT scanning showed that these areas were cal-
cifications. Anatomical locations for MSLLs and ICH were
recorded. An MR angiography or catheter angiography were
used to document intracranial large artery diseases, which
were defined as more than 50% luminal narrowings in the
internal carotid artery, anterior cerebral artery, middle ce-
rebral artery, posterior cerebral artery, basilar artery, or ver-
tebral artery. All radiographic scans were reviewed by 2 neu-
rologists (H.-J.B. and S.-H.L.), whose consensus determined
the MRI findings. The reviewers were blinded to clinical and
demographic data.

There is a growing consensus that GE-MRI may enable the
recognition of bleeding-prone microangiopathy, which has
a clinical impact because a group of individuals at high risk
of ICH, both spontaneously and following anticoagula-
tion therapy, are expected to be identifiable.6,17 Our re-
results showed that the ICH and the infarction groups dif-
fiered for the MSLL count only, providing evidence for the
possible clinical usefulness of GE-MRI.

However, it was recently indicated that MSLL did not
 discriminate between major hemorrhagic or multiple
lacunar stroke.17 Also, considering the close link be-
both ICH and ischemic injury with leukoarios-
is,1,9,18,21 and the increasing MSLL numbers with advanced leukoariosis10,11 as shown by our results, there
remains a case for determining whether GE-MRI can be
used for identifying patients at high risk of ICH in the
presence of advanced leukoariosis. Our study revealed
that, when patients have no or mild leukoariosis, 1 in-
crement of the MSLL count approximately doubled the
risk of ICH over infarction (adjusted OR = 2.46). On the
contrary, MSLLs on GE-MRI was not a predictor of ICH
 vs infarction in patients with advanced leukoariosis. These
results were unchanged when we performed statistical
analysis after excluding patients with strokes of mecha-
isms other than small vessel disease (data not shown).

We believe that in the evaluation of GE-MRI for a bleed-
ing-prone microangiopathy, the extent of leukoariosis
should always be considered.

Why did the GE-MRI lose discriminating power be-
tween ICH and infarction in those patients with advanced
leukoariosis? In the advanced leukoariosis group most of
those with large or small artery infarctions had MSLLs,
which formed a striking contrast to the GE-MRI findings
of absent MSLLs in those with infarction in the no or mild
leukoariosis group. When one considers the higher num-
bers of both lacunae and MSLLs in patients with ad-
advanced leukoariosis than in those patients with no or mild
leukoariosis, it is probably the case that arteriosclerotic changes related to long-standing exposure to stroke risk factors as the shared causative basis9 may have resulted in both occlusion and rupture.5,22,23 For example, the cerebral complications of patients with hypertension may vary; either rupture or occlusion of the diseased small artery may result in parenchymal hemorrhage, lacunar infarction, or widespread leukoariosis depending on the circumstances.5,7,23 In support of these, pathologic changes in ICH such as lipohyalinosis,7 microaneurysms,15 and fibrinoid degeneration21 have also been found in subjects with chronic hypertension, lacunae, and leukoariosis.9 Clinically silent ischemic lesions as well as previous hemorrhages are a common finding on the MRIs of patients with primary intracerebral hematomas.1 Prior ischemic infarction was also reported to be one of the risk factors for intracerebral hemorrhage.6,9,12 Moreover, some have argued10,27 and supported27 that ICH requires an underlying ischemic lesion to set the chain of hemorrhagic events in motion.

STATISTICAL ANALYSIS

First, to determine the relationship with the extent of leuko-
ariosis, the number of MSLLs and lacunae of patients with ad-
advanced leukoariosis (early confluent or confluent) were com-
pared with those of patients with no or mild leukoariosis (ab-
sent or punctate). Second, we divided the 91 patients into 2
groups, depending on whether they had an ICH or infarction.
Various variables (demographic, MRI, and risk factors) were
compared between the ICH group and the infarction group.
The Mann-Whitney test was used for comparison of continu-
ous variables between the groups. χ² Analysis was used to com-
pare proportions between groups. Third, the ICH and infarc-
tion groups were further subdivided into the no or mild group
or the advanced leukoariosis group. The MSLL counts were
compared between the ICH and infarction groups in each of
the subdivided leukoariosis groups. We also tested for statis-
tical significance of the interaction between MSLLs and leu-
koariosis in predicting the type of stroke (ICH over infarction)
using a logistic model. Finally, in both leukoariosis groups,
multiple logistic regression analysis was used to evaluate the
relative contribution of MSLL—adjusted for age, sex, and
lacunae—in discriminating between an ICH and an infarction.
Age, MSLL(s), and the numbers of lacunae were used as con-
tinuous variables; sex was analyzed as a dummy variable.

Statistical significance was set at P < .05. The Statisti-
cal Package of Social Sciences (Version 8.0; SPSS, Chi-
cago, Ill) was used for data analysis. All values are given as
the mean (SD).

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Patients With Ischemic Stroke

Several considerations must be given to our study. First, although consecutively collected, the hospital-based stroke cases of relatively small sample size in this study may not be representative of the total patient population. Although the distribution pattern of ICH and infarction subtypes in this study were similar to those of previous reports, the relatively small number of patients with ICH in the advanced leukoariosis group still remains as a weak point. Second, we did not exclude patients with territorial infarctions or lobar hemorrhages, and this nonhomogeneity of subjects may have altered our results in some way. However, we believe that the study group is closer to and more representative of the actual clinical situation, in which patients with small artery disease are not free from ICH or infarction due to large artery disease or cerebral amyloid angiopathy. Except for 4 cases, large artery disease was preponderantly observed in the infarction group, which is consistent with the findings of previous reports. The MSLL can represent underlying amyloid angiopathy in cases of lobar ICH, but the frequencies of lobar ICH in the no or mild leukoariosis group were similar to those seen in the advanced leukoariosis group. In addition, there were only a few patients with lobar ICH who had

Table 1. Demographic, Magnetic Resonance Imaging (MRI) and Angiography, and the Risk Factor Variables of Patients With Ischemic Infarction and Intracerebral Hemorrhagic (ICH) Strokes*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ischemic Infarction Stroke (n = 58)</th>
<th>ICH Stroke (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64.2 (10.4)</td>
<td>64.3 (9.7)</td>
</tr>
<tr>
<td>Male sex, % (No.)</td>
<td>65.5 (38)</td>
<td>60.6 (20)</td>
</tr>
<tr>
<td>MRI and MR angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocal signal loss lesions†</td>
<td>3.9 (13.5)</td>
<td>8.9 (13.4)</td>
</tr>
<tr>
<td>No. of lacunae</td>
<td>3.7 (4.2)</td>
<td>3.6 (3.7)</td>
</tr>
<tr>
<td>Presence of advanced leukoariosis, % (No.)</td>
<td>29.3 (17)</td>
<td>39.4 (13)</td>
</tr>
<tr>
<td>Large artery disease, % (No.)‡</td>
<td>55.2 (32)</td>
<td>12.1 (4)</td>
</tr>
<tr>
<td>Risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, % (No.)</td>
<td>79.3 (46)</td>
<td>93.9 (31)</td>
</tr>
<tr>
<td>Diabetes mellitus, % (No.)</td>
<td>25.9 (15)</td>
<td>18.2 (6)</td>
</tr>
<tr>
<td>Smoking, % (No.)</td>
<td>34.5 (20)</td>
<td>27.3 (9)</td>
</tr>
<tr>
<td>Cholesterol level, mg/dL§</td>
<td>186.0 (48)</td>
<td>191.1 (34)</td>
</tr>
<tr>
<td>Hypocholesterolemia (&lt;160 mg/dL), % (No.)</td>
<td>28.1 (16)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;239 mg/dL), % (No.)</td>
<td>10.5 (6)</td>
<td>6.7 (2)</td>
</tr>
<tr>
<td>Previous medication use, % (No.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>6.9 (4)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>1.7 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>29.3 (17)</td>
<td>24.2 (8)</td>
</tr>
</tbody>
</table>

*Values are given as mean (SD) unless otherwise indicated.
†P<.001, Mann-Whitney test.
‡P<.001, χ² test.
§The cholesterol level was not checked in 4 patients.
||To convert to millimoles per liter multiply by 0.02586.

Table 2. Logistic Regression Analysis of Stroke Type (Intracerebral Hemorrhage vs Ischemic Infarction) When Leukoariosis Is Classified as None or Mild

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.332</td>
<td>0.242-7.330</td>
<td>.74</td>
</tr>
<tr>
<td>Age</td>
<td>1.005</td>
<td>0.907-1.113</td>
<td>.93</td>
</tr>
<tr>
<td>No. of lacunae</td>
<td>0.799</td>
<td>0.529-1.207</td>
<td>.29</td>
</tr>
<tr>
<td>No. of multifocal signal loss lesions</td>
<td>2.461</td>
<td>1.381-4.387</td>
<td>.002</td>
</tr>
</tbody>
</table>

*The variables tested for sex, age, number of lacunae, and number of multifocal signal loss lesions. χ² (likelihood ratio test of the model) = 29.41, P<.001.
The number of MSLls on GE-MRI is a predictor of ICH vs infarction in patients with no or mild leukoariosis, but not in those with advanced leukoariosis. A GE-MRI, if used alone to decide on different types of secondary prevention for stroke, without consideration of the extent of leukoariosis, may act as a "double-edged sword" affording a prediction of hemorrhagic complications at the no or mild leukoariosis classification and raising the possibility of relapsing ischemic stroke in the case of advanced leukoariosis.

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Author contributions: Study concept and design (Drs D.-E. Kim, Bae, Lee, H. Kim, and Roh); acquisition of data (Drs Bae, Lee, and Yoon); analysis and interpretation of data (Drs D.-E. Kim and H. Kim); drafting of the manuscript (Drs Bae, Lee, and Yoon); critical revision of the manuscript for important intellectual content (Drs D.-E. Kim, H. Kim, and Roh); statistical expertise (Dr H. Kim); administrative, technical, and material support (Dr D.-E. Kim); study supervision (Drs Bae and Yoon and Roh).

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REFERENCES


Table 3. Locations for Multifocal Signal Loss Lesions (MSLs)*

<table>
<thead>
<tr>
<th>Leukoariosis</th>
<th>Type of Lesion</th>
<th>MSLs†</th>
<th>Total</th>
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<tbody>
<tr>
<td>None or mild</td>
<td>Deep hemorrhage</td>
<td>2/5</td>
<td>9/6</td>
</tr>
<tr>
<td></td>
<td>Lobar hemorrhage</td>
<td>5/9</td>
<td>1/2</td>
</tr>
<tr>
<td></td>
<td>Small artery infarct</td>
<td>13/14</td>
<td>1/0</td>
</tr>
<tr>
<td>Advanced</td>
<td>Large artery infarct</td>
<td>15/16</td>
<td>2/1</td>
</tr>
<tr>
<td></td>
<td>Deep hemorrhage</td>
<td>4/4</td>
<td>6/6</td>
</tr>
<tr>
<td></td>
<td>Lobar hemorrhage</td>
<td>1/0</td>
<td>1/2</td>
</tr>
<tr>
<td></td>
<td>Small artery infarct</td>
<td>1/2</td>
<td>9/8</td>
</tr>
<tr>
<td></td>
<td>Large artery infarct</td>
<td>1/4</td>
<td>3/0</td>
</tr>
<tr>
<td>Total</td>
<td>42/48</td>
<td>32/26</td>
<td>74</td>
</tr>
</tbody>
</table>

*Distribution of the patients in the 2 leukoariosis groups is subdivided by stroke locations.
†Values are given by number of patients with deep/lobar (both deep and lobar) MSLs. Seventeen patients with infarctonal strokes (13 infarctions and 4 hemorrhages) are omitted.
‡Large and small artery infarcts were classified according to the criteria of the Trial of Org10172 in Acute Stroke Treatment (TOAST).12


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