Clinical Significance of Microbleeds in Subcortical Vascular Dementia

Sang Won Seo, MD; Byung Hwa Lee, MA; Eun-Joo Kim, MD, PhD; Juhee Chin, MA; Yoon Sun Cho, MS; Uicheul Yoon, PhD; Duk L. Na, MD, PhD

Background and Purpose—Despite many studies investigating the association between the ischemic changes and cognitive impairment in subcortical vascular dementia (SVaD), few studies correlated cognitive impairment with microbleeds (MBs) frequently seen in SVaD.

Methods—Participants consisted of 86 patients with SVaD who fulfilled the criteria proposed by Erkinjuntti et al.

Results—MBs occurred in 73 of 86 (84.9%) patients with SVaD. MBs were most commonly distributed in the cortex, and the cortical MBs were most pronounced in the temporoparietal area. A multiple regression showed that the number of cerebral MB was an independent predictor of cognitive impairment in multiple domains and the severity of dementia even after controlling confounding factors such as age, education, ischemic severity, and number of lacunes.

Conclusion—These results indicate that cerebral MB is one of the important factors that cause cognitive impairments in SVaD. (Stroke. 2007;38:1949-1951.)

Key Words: cognitive impairment □ microbleeds □ vascular dementia

Cognitive impairment in subcortical vascular dementia (SVaD) probably results from ischemic interruption of frontal subcortical circuits. Thus, SVaD is preferentially called subcortical ischemic vascular dementia. With recent advent of T2* gradient-echo MRI (GE-MRI), however, many studies demonstrated that small vessel disease can produce not only ischemia but also microbleeds (MBs),1,2 suggesting that patients with SVaD have the comorbidity of ischemia and MBs. Nonetheless, the clinical significance of MBs in SVaD has not been studied yet. The objective of this study was to examine the relationships between the number of MBs and the cognitive deficits in SVaD.

Methods

Patients
We retrospectively found 86 patients from our memory disorder clinic who met the clinical and imaging criteria of SVaD proposed by Erkinjuntti et al.,3 and had undergone GE-MRI in our hospital. All the patients underwent a clinical interview, neurological examination, and a battery of neuropsychological tests which has been previously described.4 The study was approved by Institutional Review Board of the hospital.

Ischemia and Lacune Rating on MRI
Two neurologists blinded to clinical information scored the extent of ischemic changes of deep and periventricular white matter using a semiquantitative scale proposed by Scheltens et al.6 Because lacunes in deep gray matter can be associated with number of MBs,6 lacunes were counted in basal ganglia and thalamus. The lacunar infarction was defined as a small lesion (<15 mm in diameter) with low signal on T1-, high signal on T2-weighted images, and perilesional halo on fluid-attenuated inversion recovery images.

Analysis of MBs on GE-MRI
The same neurologists made a consensus on the number and location of MBs on 20 axial slices of GE-MRI that had been obtained as previously described.7 The MB was defined as a homogeneous round signal loss lesion with a diameter ≤10 mm on the GE-MRI. Hypointense lesions within the subarachnoid space, or those possibly associated with calcification, traumatic brain injury or vascular malformation were excluded.

Results

Frequency and Distribution of MBs
Details of demographic and MRI findings of the patients are presented in Table 1. MBs occurred in 73 of 86 (84.9%) patients. The total number of MBs in the 73 patients was 4147 and the number of MBs per patient ranged from 1 to 613 with a median number of 13. MBs were most commonly distributed in the cortex (Table 2), and the cortical MBs were most pronounced in the temporoparietal area (Figure).

Effects of Cerebral MBs on Cognition and Dementia Severity
To assess the clinical impact of cerebral MBs on cognition and dementia severity, we performed a linear regression after controlling confounding factors such as age, education, ischemic severity, and number of lacunes.
controlling age, education, the severity of ischemia, and the number of lacunes. The number of cerebral MBs served as an independent variable whereas scores of neuropsychological tests, Mini-Mental State Examination and Clinical Dementia Rating served as dependent variables. The results showed that the number of cerebral MBs was an independent predictor of cognitive impairments in the following cognitive domains: attention (the digit span-backward \( t = -2.672, P = 0.010 \)), verbal memory (sum of 3 free recall trials of Seoul Verbal Learning test [SVLT] \( t = -2.134, P = 0.037 \), SVLT-delayed recall \( t = -2.134, P = 0.038 \), and SVLT-recognition test \( t = -2.656, P = 0.010 \)), visual memory (Rey-Osterrieth Complex Figure test [RCFT]-recognition test \( t = -2.274, P = 0.027 \)), language (Boston Naming Test \( t = -1.913, P = 0.061 \), marginally significant), visuospatial function (RCFT-copying \( t = -2.183, P = 0.033 \)), and frontal executive function (semantic Controlled Oral Word Association Test [COWAT] \( t = -2.589, P = 0.012 \)). The number of cerebral MBs was also an independent predictor of dementia severity: Mini-Mental State Examination \( t = -2.201, P = 0.032 \) and Clinical Dementia Rating \( t = 1.989, P = 0.052 \), marginally significant).

**Discussion**

Our study showed that MBs are very frequent in patients with SVaD (84.9%). There had been 2 studies that investigated MBs in patients with vascular dementia.8,9 One study enrolled 31 white subjects with vascular dementia (not necessarily SVaD) and reported the frequency of MB of 65%,8 which is comparable to the frequency of MB we found in our study (84.9%).

**TABLE 1. Demographic and MRI Findings of Patients (n=86)**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>69.6 ± 8.4</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>34/86 (39.5%)</td>
</tr>
<tr>
<td>Education, years</td>
<td>8.4 ± 5.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65/86 (75.6%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28/86 (32.6%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>30/86 (34.9%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>6/86 (7.0%)</td>
</tr>
<tr>
<td>Use of antithrombotic medication</td>
<td>33/86 (38.4%)</td>
</tr>
<tr>
<td>Ischemic score (white matter)</td>
<td>17.6 ± 3.4</td>
</tr>
<tr>
<td>Frontal</td>
<td>5.6 ± 0.9</td>
</tr>
<tr>
<td>Parietal</td>
<td>5.0 ± 0.9</td>
</tr>
<tr>
<td>Temporal</td>
<td>1.1 ± 1.5</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.2 ± 1.0</td>
</tr>
<tr>
<td>No. of lacune</td>
<td>4.8 ± 3.9</td>
</tr>
</tbody>
</table>

A, An illustration of GE-MRI of a typical patient who showed severe cortical MBs predominantly in temporo-parietal area. B, To illustrate the distribution of cortical MBs, cortical MBs on axial scans of GE-MRI from all patients were depicted on the glass brain of a single subject.
lower than our frequency. This difference may be attributable to an ethnic difference as has been reported in a previous study.\(^1\) Even considering this ethnic factor, however, our frequency was higher than a study (frequency: 77\%, and number of MBs ranging from 1 to 85) that involved an Asian SVaD patients.\(^9\) This difference may be explained by more severe ischemic changes in our study (MRI criteria of Erkinjuntti versus Fazekas grade 3) and greater number of GE-MRI scan slices (20 versus 12).\(^9\)

Clinical implications of MBs have rarely been studied. A recent review article suggested that the cognitive impairment of patients with cerebral amyloid angiopathy might be a associated with the number of baseline hemorrhages.\(^2\) Another study recruited patients with stroke (not vascular dementia) and found that patients with MBs were more impaired at frontal executive functions than those without MBs, and postulated that MBs located in the frontal lobe and the basal ganglia might have caused it.\(^10\) Unlike this study, our study involving patients only with SVaD showed that the number of cerebral MBs is the predictive factor of impairment in multiple cognitive domains. Furthermore, MBs affected the general cognitive dysfunction and the severity of dementia in SVaD. These effects were present even after controlling age, education, ischemic changes and lacunes on MRI. Thus, our results suggest that not only ischemia but also microhemorrhages are primary pathomechanisms of cognitive impairment. Histopathological data that MBs involve not only hemosiderin deposition but also surrounding gliosis and frank necrosis or infarction also support the clinical importance of MBs.\(^11\)

Our study has limitations. Because the diagnosis was not confirmed by pathology, we cannot exclude the possibility that Alzheimer disease or cerebral amyloid angiopathy is combined in our patients.

Sources of Funding
This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A050079).

Disclosures
None.

References

TABLE 2. Distribution MBs in Patients

<table>
<thead>
<tr>
<th>No. of MBs</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Temporal</th>
<th>Occipital</th>
<th>White Matter</th>
<th>Basal Ganglia</th>
<th>Thalamus</th>
<th>Brain Stem</th>
<th>Cerebellum</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>742</td>
<td>732</td>
<td>1131</td>
<td>425</td>
<td>168</td>
<td>383</td>
<td>296</td>
<td>106</td>
<td>164</td>
<td>4147</td>
</tr>
</tbody>
</table>
Clinical Significance of Microbleeds in Subcortical Vascular Dementia
Sang Won Seo, Byung Hwa Lee, Eun-Joo Kim, Juhee Chin, Yoon Sun Cho, Uicheul Yoon and Duk L. Na

Stroke. 2007;38:1949-1951; originally published online May 17, 2007;
doi: 10.1161/STROKEAHA.106.477315

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/38/6/1949

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/