Risk Factors for Silent Cerebral Infarcts in Subcortical White Matter and Basal Ganglia

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Background and Purpose—The purpose of this study was to clarify whether the relevant risk factors for silent cerebral infarcts (SCIs) in subcortical white matter (WM) are different from those in the basal ganglia (BG).

Methods—Subjects of this study were 219 adults without a history of stroke or transient ischemic attack and without any abnormality on a neurological examination who consecutively visited the neurology service in our hospital between January 1994 and November 1997 requesting medical evaluation for possible cerebrovascular diseases. Subjects included 141 men and 78 women ranging in age from 33 to 83 years (mean ± SD, 63.2 ± 9.5 years). We performed brain MRIs and cervical/cranial magnetic resonance angiographies on all subjects. In this study, SCI was defined as a focal lesion >5 mm in diameter that was prolonged on both T2-weighted and proton density images.

Results—SCIs in the WM and/or BG were detected in 88 (40.2%) of the 219 subjects. No SCI >15 mm was observed in this series. Fifty of the subjects had SCIs only in the WM, 32 subjects had SCIs in both the WM and BG, and 6 subjects had SCIs only in the BG. Thus, 82 (93.2%) of 88 subjects with SCIs had lesions in the WM. Most subjects with SCIs in the BG also had SCIs in the WM. Multiple logistic regression analyses revealed that age, female sex, and hypertension were significant and independent predictors of SCIs in the WM, and that age, a history of ischemic heart disease, and carotid artery stenosis were significant and independent predictors of SCIs in the BG.

Conclusions—The present study indicated that the relevant risk factors for SCIs in the WM and those for SCI in the BG were different. Our results suggest that SCIs are prone to first appear in the WM in association with aging and hypertension, and the additional appearance of SCIs in the BG predicts a progression of generalized atherosclerosis that is manifested in the carotid and coronary arteries. (Stroke. 1999;30:378-382.)

Key Words: infarcts, silent ■ magnetic resonance angiography ■ magnetic resonance imaging ■ risk factors

Silent cerebral infarcts (SCIs) are frequently demonstrated in the subcortical white matter (WM) or the basal ganglia (BG) in stroke patients and elderly subjects by CT and MRI. Those with SCIs are generally considered to be a high-risk group for clinical stroke. Several studies have examined the incidence of SCIs and its relation to risk factors for stroke. The majority of these studies demonstrated that age and hypertension are significantly related to stroke. However, the underlying vascular pathology for ischemia is reportedly different between the WM and BG. Sclerotic changes of the medullary arteries supplying the WM were primarily fibrohyaline thickenings of the wall, while those of the perforating arteries in the BG were of various forms. Accordingly, it is conceivable that the relevant risk factors are different between SCIs in the WM and SCIs in the BG. We therefore performed MRI examinations in subjects without a history of stroke or transient ischemic attack and examined separately the associated risk factors for SCIs in the WM and BG.

Subjects and Methods

The subjects of this study were 219 adults without a history of stroke or transient ischemic attack and without any abnormality on a neurological examination who consecutively visited the clinic of the neurology service of Hyogo Brain and Heart Center at Himeji, Japan, between January 1994 and November 1997. These subjects requested medical evaluation for possible cerebrovascular diseases for reasons such as simple fear of stroke, positive family history of stroke, and vascular risk factors. Although some of these subjects complained of nonspecific subjective symptoms such as headache and dizziness, those with migraine, those with vertigo possibly caused by brain stem or cerebellar dysfunction, and those who had a contraindication for MR study were not included. Subjects were carefully checked for their medical history and given a complete neurological examination. They included 141 men and 78 women ranging in age from 33 to 83 years (mean ± SD, 63.2 ± 9.5 years). Informed consent was obtained from all subjects.

We performed brain MRI and MR angiography (MRA) on all subjects. All examinations were performed with a 1.0-T MR system (Magnetom Impact, Siemens). T1-weighted images (repetition time, 500 ms; echo time, 15 ms), T2-weighted images (repetition time, 2000 ms; echo time, 80 ms), and proton density images (repetition time, 2000 ms; echo time, 20 ms) were obtained in the transverse...
plane with 8-mm-thick sections. An SCI was defined as a focal lesion >5 mm in diameter that was prolonged on both T2-weighted and proton density images. Periventricular hyperintense lesions and subcortical patchy or confluent hyperintense lesions were not included. When distinction between such lesions and infarcts was ambiguous, we used T1-weighted images, in which infarcts are primarily presented with hypodensity. We recorded the presence of ≥1 SCI in the territory of the carotid artery system in each subject.

The location was coded separately as WM or BG. MRA acquisition and reconstruction are described elsewhere. The extracranial portion of the internal carotid artery (ICA) was evaluated with cervical MRA. To measure the percent stenosis of the extracranial portion of the ICA, we compared the diameter with that of the normal-appearing proximal ICA beyond the carotid bulb. The intracranial arteries were evaluated with intracranial MRA for the intracranial portion of the ICA and the horizontal portion of the middle cerebral artery (MCA). We rated occlusive lesions for each arterial portion by giving them 1 of 5 grades depending on the narrowness of the arteries, ie, normal, mild, moderate, severe, and occluded according to an established scoring scheme. In this scoring scheme, <25% reduction of an arterial diameter was graded as normal, 25% to 49% reduction was graded as mild stenosis, 50% to 74% reduction was graded as moderate stenosis, 75% to 99% reduction was graded as severe stenosis, and no opening was graded as occlusion. Two investigators (T.U., M.T.), under blinded conditions for all clinical information, independently reviewed the MRIs and MRAs. When there was disagreement, the final decision was made through a consensus meeting with a third investigator (E.M.). Interrater reliability and accuracy are good for evaluating stenoses of >25% narrowing in the cervical carotid artery and specific segments of the intracranial arteries. For the carotid bifurcation, the reliability (k=0.89) and accuracy are comparable to those of conventional angiography. For the intracranial arteries, substantially high interrater reliability (k=0.85) and specificity (>85%) have been achieved as well as a sensitivity of 100%.

Hypertension, diabetes mellitus, hyperlipidemia, smoking habit, and ischemic heart disease (IHD) were evaluated as risk factors. Hypertension was judged as present when either systolic pressure of >160 mm Hg or diastolic pressure of >95 mm Hg was demonstrated on repeated examinations or when there was a history of treatment for hypertension. Diabetes mellitus was judged as present when a fasting blood glucose level was >140 mg/dL or when there was a history of treatment for diabetes mellitus. Hyperlipidemia was judged as present when laboratory examination of the serum at presentation showed a total cholesterol level of >220 mg/dL, a triglyceride level of >150 mg/dL, an HDL cholesterol level of <40 mg/dL, or when there was a history of treatment. IHD was judged as present when there was a history of myocardial infarction or angina pectoris.

Effects of the predictive variables on SCIs were preliminarily analyzed with Fisher exact probability test or Student’s t test. Multiple logistic regression analysis was used to estimate independent effects of the predictive variables on SCIs. The analysis was repeated for each of the SCIs in the WM and BG, with each abnormality as a dependent variable and with patients’ background characteristics, including possible risk factors and cerebral artery occlusive lesions, as independent variables. All statistical analyses were performed with SAS Release 6.10 software. The level of significance was set at P<0.05 for all statistical analyses.

### Results

SCIs were detected in the WM and/or BG of 88 (40.2%) of the 219 subjects and increased with advancing age (Figure). Of the 88 subjects with SCIs, 50 had SCIs only in the WM, 32 had SCIs in both the WM and BG, and 6 had SCIs only in the BG. Thus, 82 (93.2%) of 88 subjects with SCIs had lesions in the WM. Most of the subjects with SCIs in the BG also had SCIs in the WM. No patient had cortical lesions. No SCI >15 mm was observed.

Of the 219 subjects, 102 (46.6%) were hypertensive, 37 (16.9%) were diabetic, 76 (34.7%) were hyperlipidemic, 88 (40.2%) had a smoking habit, and 63 (28.8%) had IHD.

The MRA examinations indicated that 24 subjects (11.0%) had stenoses in the cervical carotid artery. Of these 24 subjects, 15 had a mild stenosis, 6 had a moderate stenosis, 2 had a severe stenosis, and 1 had an occlusion. Stenoses in the intracranial artery were found in 30 subjects (13.7%). Of these 30 subjects, 20 had a mild stenosis, 4 had a moderate stenosis, 5 had a severe stenosis, and 1 had an occlusion. Seven subjects had lesions in both the cervical carotid and intracranial arteries. Thus, the MRAs showed evidence of cerebral arterial stenoses in 46 subjects (21.0%).

The patients’ characteristics, including possible risk factors and cerebral arterial occlusive lesions, are summarized for SCIs in the WM in Table 1 and for SCIs in the BG in Table 2. Patients with SCIs in the WM were significantly older and had significantly higher prevalence of female sex, hypertension, diabetes mellitus, carotid artery stenosis, and intracranial artery stenosis than those without SCI in the WM. Compared with patients without SCIs in the BG, those with SCIs in the BG were significantly older and had significantly higher prevalence of hyperlipidemia, IHD, carotid artery stenosis, and intracranial artery stenosis. Multiple logistic regression analyses revealed that age, female sex, and hypertension were significant and independent predictors of SCIs in the WM (Table 3) and that age, IHD, and carotid artery stenosis were significant and independent predictors of SCIs.
TABLE 2. Characteristics of Patients With SCI in BG

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SCI in BG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (n=38)</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>68.8±6.2</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>23/15</td>
</tr>
<tr>
<td>Hypertension (present/absent)</td>
<td>23/15</td>
</tr>
<tr>
<td>Diabetes mellitus (present/absent)</td>
<td>6/32</td>
</tr>
<tr>
<td>Smoking habit (present/absent)</td>
<td>13/25</td>
</tr>
<tr>
<td>IHD (present/absent)</td>
<td>21/17</td>
</tr>
<tr>
<td>Carotid artery stenosis (present/absent)</td>
<td>11/27</td>
</tr>
<tr>
<td>Intracranial artery stenosis (present/absent)</td>
<td>10/28</td>
</tr>
</tbody>
</table>

in the BG (Table 4). To clarify whether the relationship between SCIs in the BG and carotid artery stenosis contributes to the direct effects from carotid artery stenosis, prevalence of SCIs in the BG on the side of the carotid artery lesion and prevalence on the nonlesioned side were compared among 24 subjects with carotid artery lesions. The prevalence of SCIs in the BG on the side of the carotid artery lesion (13/33, 39.4%) was not significantly different from that on the side without the carotid lesion (5/15, 33.3%) (P=0.472, Fisher exact test).

Discussion

Although hyperintense areas on T2-weighted MR images represent infarcts, dilated perivascular spaces (Virchow-Robin spaces), gliosis, and demyelination,13–15 infarcts from other causes were carefully determined by using a size definition of ≥5 mm in diameter14 and proton density-weighted MR images, which reportedly differentiate lacunar infarcts from dilated perivascular spaces.15 The additional confirmation of hypodensity on T1-weighted images was applied to distinguish infarcts from diffuse WM disease. The MRA imaging technique and the stenosis rating scheme used in the present study have also been validated in comparative studies with conventional angiography.9,10

The prevalence of SCIs in the former CT or MRI studies of first-ever stroke patients varied from 10% to 38%.1,2,16–18 According to large population-based studies using MRI, the prevalence of SCIs is 11% to 28%.19–21 In the present hospital-based study, the frequency of SCIs was 40.2%. It should be noted that this frequency refers to this particular selected population rather than a true prevalence, since it is impossible to exclude referral or selection bias in this type of hospital-based study. The subjects studied were considered at high risk because they were specifically concerned about stroke for various reasons, including positive family history and vascular risk factors. The prevalence of SCIs would be subject to the sample constitution, eg, age, sex, race, ethnicity, and involved risk factors. In addition, the results would be affected by the sensitivity and specificity of the examination and the diagnostic criteria of SCIs used in each study. The frequency of SCIs in our study was comparable to those reported in MRI-based studies used in Japan. Hougaku et al4 reported a frequency of 42% in 117 patients who had ≥1 stroke risk factor, and Shimada et al22 reported a frequency of 47% in 73 elderly patients.

Multiple logistic regression analyses showed that age, female sex, and hypertension were significant and independent predictors of SCIs in the WM and that age, IHD, and carotid artery stenosis were significant and independent predictors of SCIs in the BG. These findings support the assumption that the risk factors for SCIs in the WM and BG are different. Although univariate analyses demonstrated that diabetes mellitus, carotid artery stenosis, and intracranial artery stenosis were associated with SCIs in the WM and that hyperlipidemia and intracranial artery stenosis were associated with SCIs in the BG, these associations were not found in multiple logistic regression analyses. These associations noted in univariate analyses were likely to be discounted by interaction among factors, especially by correlations with age. Although it has been reported that smoking habit is associated with SCIs in large population-based studies,19,21 this finding was not replicated in our study. This lack of association may be attributable to the relatively small sample size of our study.

The majority of previous studies1–3,6,7,21 demonstrated that age and hypertension strongly and independently correlated with SCIs. As in previous studies, the present study demonstrated that age was a common risk factor for SCIs in both the WM and BG. However, in our study hypertension was a significant factor for SCIs in the WM but not in the BG. These results, together with the fact that most of cases with

TABLE 3. Possible Predictors of SCI in WM

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Cl</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (by 1 year)</td>
<td>1.101</td>
<td>1.051–1.153</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.285</td>
<td>0.119–0.686</td>
<td>0.0051</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.970</td>
<td>1.010–3.843</td>
<td>0.0467</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.346</td>
<td>0.979–5.622</td>
<td>0.0558</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.593</td>
<td>0.786–3.229</td>
<td>0.1968</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>1.775</td>
<td>0.748–4.213</td>
<td>0.1929</td>
</tr>
<tr>
<td>IHD</td>
<td>0.697</td>
<td>0.420–1.915</td>
<td>0.7793</td>
</tr>
<tr>
<td>Carotid artery stenosis</td>
<td>2.680</td>
<td>0.903–7.956</td>
<td>0.0757</td>
</tr>
<tr>
<td>Intracranial artery stenosis</td>
<td>1.790</td>
<td>0.684–4.689</td>
<td>0.2358</td>
</tr>
</tbody>
</table>

TABLE 4. Possible Predictors of SCI in BG

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Cl</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (by 1 year)</td>
<td>1.090</td>
<td>1.028–1.156</td>
<td>0.0040</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.081</td>
<td>0.397–2.944</td>
<td>0.8789</td>
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<tr>
<td>Hypertension</td>
<td>1.893</td>
<td>0.819–4.375</td>
<td>0.1534</td>
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<tr>
<td>Diabetes mellitus</td>
<td>0.726</td>
<td>0.249–2.116</td>
<td>0.5569</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2.318</td>
<td>0.979–5.488</td>
<td>0.0558</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>0.582</td>
<td>0.210–1.613</td>
<td>0.2983</td>
</tr>
<tr>
<td>IHD</td>
<td>2.613</td>
<td>1.136–6.014</td>
<td>0.0239</td>
</tr>
<tr>
<td>Carotid artery stenosis</td>
<td>3.246</td>
<td>1.116–9.444</td>
<td>0.0307</td>
</tr>
<tr>
<td>Intracranial artery stenosis</td>
<td>0.771</td>
<td>0.275–2.158</td>
<td>0.6198</td>
</tr>
</tbody>
</table>

Data show the results of multiple logistic regression analysis.
SCIs in the BG also had SCIs in the WM, suggest that SCIs initially appear in the WM in association with aging and hypertension and subsequently appear in the BG in association with development of atherosclerosis because hypertension accelerates the pathological process in the medullary arteries supplying the WM.8

We found a significant correlation between SCIs in the WM and female sex. In a large population-based study, a correlation between SCIs and female sex has been demonstrated.21 However, male sex has been noted as a risk factor for SCIs in some studies.1,2,16 Although the association with female sex was restricted to SCIs in the WM, the reason for the discrepancy among studies is not clear. This finding should be confirmed in further studies.

Carotid artery stenosis was a significant and independent predictor of SCIs in the BG. This finding was consistent with the findings of previous reports.5,21,23 In studies of symptomatic lacunar infarction, it has been pointed out that ipsilateral carotid stenotic lesions are potential embolic sources associated with lacunar infarction in the territory of deep perforating arteries.24,25 Ghika et al26 reported that 28 of 100 patients with symptomatic lacunar infarction in the territory of the deep perforators of the carotid system had ipsilateral carotid artery stenosis. Stenotic lesions of the ICA may also play a role in the pathogenesis of lacunes through hemodynamic effects. In an animal model study, diffuse cerebral ischemia from carotid occlusion caused infarction only in the striatum, and a possible toxic effect of dopamine release in the ischemic zone has been assumed to be related to the damage.27 The similar mechanism might be involved in human diffuse cerebral ischemia. However, in the present study SCIs in the BG were just as frequent on the contralateral side of the arterial lesions as they were on the ipsilateral side of the carotid lesions, challenging the assumption that carotid artery lesions caused these SCIs. Thus, an alternative explanation is needed. Similar to our findings, the results of Brott et al28 showed that SCIs in the setting of asymptomatic carotid stenosis were not uncommon but were evenly distributed ipsilaterally and contralaterally to the stenotic artery. Sise et al.29 analyzing the incidence of preoperative SCI in patients who underwent carotid endarterectomy, noted that SCIs were commonly found in these patients but were found on the contralateral side of the target carotid artery in more than half of the cases. They suggested that carotid plaque formation and small-vessel thrombotic events were most likely parallel phenomena related to the risk factors. Longstreth et al.21 analyzing restricted subjects with lacunes affecting only 1 side of the brain in a population-based study, reported that the correlations of stenoses were not consistently stronger for ipsilateral than for contralateral lacunes. Together with these observations, our results indicated that the appearance of SCIs in the BG was more likely to be paralleled by a background atherosclerosis than by direct effects from carotid artery stenosis.

The association between IHD and SCIs has been pointed out in a few studies.7,16,30 Our in vivo results replicated the findings of the autopsy study of Tuszynski et al,31 in which myocardial infarcts were found in 52% of patients with lacunar infarcts that were most commonly located in the BG. The appearance of SCIs in the BG likely reflects an advanced stage of systemic atherosclerosis, which is manifested in the coronary artery as well as the carotid artery.

In conclusion, the present study indicated that the relevant risk factors for SCIs in the WM and the BG were different; age, hypertension, and female sex were the risk factors for SCIs in the BG. Our results suggest that the SCIs are prone to first appear in the WM in association with aging and hypertension, and the appearance of SCIs in the BG predicts the progression of generalized atherosclerosis.

Acknowledgment
This study was supported by a research grant for cardiovascular diseases (8C-4) from the Ministry of Health and Welfare, Japan.

References
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Stroke. 1999;30:378-382
doi: 10.1161/01.STR.30.2.378
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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