Silent Cerebral Infarction as a Form of Hypertensive Target Organ Damage in the Brain

Hidetaka Hougaku, Masayasu Matsumoto, Kazuo Kitagawa, Koushi Harada, Naohiko Oku, Taiji Itoh, Hiroaki Maeda, Nobuo Handa, and Takenobu Kamada

The incidence, number, size, and location of silent cerebral infarction on 0.1 T magnetic resonance imaging was investigated in 66 hypertensive patients (63±9 years old; mean±SD) and 42 age-matched normotensive subjects (61 ±9 years old) to determine the clinical significance of hypertension in silent cerebral infarction. Cerebrovascular risk factors and the severity of hypertensive changes in other major target organs were also investigated. The incidence of silent infarction in hypertensive patients (47%) tended to be higher than that of normotensive subjects (33%) and increased significantly with advancing age. In hypertensive patients, a significantly higher incidence of silent lesions was noted in patients with hypertensive changes in major target organs (72−73% in patients with organ involvement versus 33−39% in those without). The average number of lesions in hypertensive patients was significantly higher than that in normotensive subjects (6.0 versus 2.1), and the lesions in the hypertensive patients were more frequently detected in the brain areas supplied by perforating arteries than those in normotensive subjects (47% versus 24%). These results clearly demonstrate that silent cerebral infarction is frequently seen in older hypertensive patients, especially when moderate hypertensive changes are noted in major target organs, and suggest that hypertensive arterial changes play a crucial role in the occurrence of silent infarction. (Hypertension 1992;20:816-820)

KEY WORDS • cerebral infarction • hypertension, essential • aging • magnetic resonance imaging

Evidence of old cerebral infarction on x-ray computed tomography or magnetic resonance imaging (MRI) is common in acute stroke patients without a prior history of stroke.¹-⁵ This type of stroke, called silent cerebral infarction (SCI), is considered a preclinical warning of symptomatic strokes and brain damage related to multiple deep infarcts.⁶ To prevent these further disabling diseases, it is very important to characterize and manage this preclinical stage of cerebrovascular disease.

Hypertension is the most well-known major risk factor for stroke,⁷,⁸ and it is conceivable that hypertension is closely related to the appearance of SCI. Shimada et al⁹ recently reported that ambulatory blood pressure monitoring was a useful method to predict latent cerebrovascular disease such as SCI. However, few reports have detailed the relation between SCI and hypertension.

To determine the clinical significance of hypertension in the appearance of SCI, we compared the incidence, multiplicity, and location of SCI lesions between normotensive and hypertensive patients and further tried to clarify the relation between SCI and other hypertensive target organ damage, such as hypertensive retinopathy and hypertensive cardiac and renal involvement.

Methods

From June 1988 to June 1990, 108 consecutive outpatients without a prior history of stroke were studied by MRI examination of the brain. They consisted of 66 patients with essential hypertension (63±9 years old; mean±SD) and 42 age-matched normotensive subjects (61 ±9 years old). All patients were right-handed. Careful history taking and precise examinations by neurologists revealed that no subject had neurological deficits or symptoms or a prior history of cerebral accident, including transient ischemic attack. They had undergone MRI investigation chiefly to evaluate nonspecific neurological complaints (i.e., headache, lightheadedness, dizziness). All patients gave informed consent according to the Osaka University Hospital Ethics Review Committee.

Hypertension was diagnosed when clinical blood pressure exceeded 160 mm Hg systolic/95 mm Hg diastolic with patients in the sitting position, or when patients were taking antihypertensive medication. All hypertensive patients met criteria for World Health Organization stage I or II hypertension.

The prevalence of other accepted risk factors for stroke was investigated in both groups. Selected risk factors were diabetes mellitus (fasting blood glucose >110 mg/dl, Hb A1c >6.4% or taking medication), hypercholesterolemia (serum cholesterol >220 mg/dl or...
taking medication), daily alcohol intake, daily cigarette smoking, obesity (body mass index > 25), cardiac disease (arrhythmia or ischemic heart disease), hyperuricemia (serum uric acid > 7.0 mg/dl or taking medication), and elevated hematocrit (>46%).

Hypertensive end-organ involvement was assessed in hypertensive patients by electrocardiogram, urinalysis, blood chemistry, and fundoscopy. Patients were considered to have heart involvement if there was electrocardiographic evidence of left ventricular hypertrophy, defined as abnormally high QRS complex voltage, atrial fibrillation, or depressed downsloping ST segments. Patients were considered to have renal involvement if they had proteinuria or elevated serum creatinine (≥1.2 mg/dl). Hypertensive retinopathy was classified as hypertensive change (H) and arteriosclerotic change (S) according to Scheie's classification.

MRI was performed using a field strength of 0.1 T (Siemens-Asahi MEDITEC Co., Tokyo) in the orbitomeatal plane with sections 10 mm thick, in the manner of an inversion recovery technique with a repetition time (TR) of 2,100 msec, an inversion time of 400 msec, and an echo time (TE) of 18 msec to achieve T1-weighted images and a spin echo technique (TR, 2,200; TE, 100) to achieve T2-weighted images. On magnetic resonance images, infarction was defined as a focal area with prolonged T1 and T2 relaxation times larger than 5 sec. These lesions were visible as low and high signal intensity areas on T1- and T2-weighted images, respectively. Hyperintense punctate lesions only on T2 images were not counted as infarctions to exclude small unidentified bright objects (UBOs) of little clinical importance. Lesions smaller than 5 mm detected both on T1- and T2-weighted images were also not counted to exclude enlarged perivascular spaces (état criblé), most of which were smaller than 5 mm in diameter according to Braffman et al. The brain was divided into nine areas on the basis of the atlas Neuanoatomie der kraniiien Computerstomographie as follows: the basal ganglia, internal capsule, thalamus, semioval center, frontal lobe, temporal lobe, occipital lobe, parietal lobe, and infratentorial area. We defined the semioval center as a rather narrow area supplied by the perforating arteries (Figure 1). The periventricular hyperintensity area was excluded from the infarction criteria of this study. All magnetic resonance images were evaluated by two neuroradiologists.

Table 1. Incidence of Risk Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Incidence (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HT</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>54</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>57*</td>
</tr>
<tr>
<td>Elevated hematocrit</td>
<td>28</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>39</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>42</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>15</td>
</tr>
<tr>
<td>Obesity</td>
<td>27</td>
</tr>
</tbody>
</table>

HT, hypertensive patients; NT, normotensive subjects. *p<0.05 vs. NT.

The χ² test and unpaired t test were used to analyze results.

Results

Table 1 shows the incidence of stroke risk factors in all subjects. The incidence of each risk factor was generally higher than previous reports because these subjects were not representative of the general population but of our outpatients. The incidence of hyperuricemia in hypertensive patients was significantly higher than that of normotensive subjects (p<0.05), but no significant differences between patients with and without hypertension were noted in the remaining risk factors.

SCI was found in 45 of 108 subjects studied (42%). A total of 216 SCI lesions was detected. All of the SCI lesions were localized in the subcortical white matter or in the basal ganglia; there were no lesions in the internal capsule or cortical areas. One lesion was located in the infratentorial area (right cerebellum) (Table 2). The distribution of lesions was slightly greater in the right hemisphere in comparison with the left (113 versus 103), but the difference was not significant. All lesions were smaller than 3 cm in diameter, with 201 lesions (93%) smaller than 1 cm (Table 3). There were no differences in lesion size between the two hemispheres.

The incidence of SCI tended to be higher in hypertensive patients (47%) than in normotensive subjects (33%). The incidence increased significantly with advancing age in hypertensive patients from 27% in the...
TABLE 3. Size of Silent Lesions

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9</td>
<td>201 (93)</td>
</tr>
<tr>
<td>10-19</td>
<td>12 (6)</td>
</tr>
<tr>
<td>20-29</td>
<td>3 (1)</td>
</tr>
<tr>
<td>≥30</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>216 (100)</strong></td>
</tr>
</tbody>
</table>

50s, 44% in the 60s, and 87% in the 70s ($p<0.01$), whereas no significant increase was noted in normotensive subjects (Figure 2).

In the evaluation of the relation between SCI incidence and hypertensive end-organ involvement, SCI was more frequent in patients who had end-organ damage (heart, kidney, ocular fundi) (Figure 3). The incidence of SCI was 72–73% in patients with other organ involvement versus 33–39% in those without it, whereas no significant difference was found between the two groups with and without ocular fundi damage (H).

Figure 4 shows the relation between SCI incidence and organ involvement assessed in advancing age decades (50s, 60s, and 70s). In the 50s, the incidence of SCI tended to be higher in patients with heart and kidney involvement (50% and 60%, respectively) than in patients without such involvement. In the 60s, the incidence was significantly higher in patients with heart and ocular fundi (S) damage. This was not clear in the 70s because patients without organ involvement had a relatively high incidence of SCI lesions. The average number of SCI lesions was significantly higher in hypertensive patients than in normotensive subjects (mean, 6.0 versus 2.1; $p<0.05$). In hypertensive patients, the average number of SCI lesions was 5.8 in the 50s, 6.2 in the 60s, and 6.0 in the 70s; in normotensive subjects, the average was 2.0 in the 50s, 2.0 in the 60s, and 3.3 in the 70s ($p<0.05$, respectively). There were no differences in lesion size between normotensive and hypertensive subjects. The increased SCI lesions in hypertensive patients were mainly distributed in the area of perforating arteries.

As for the incidence of risk factors for stroke, patients with SCI showed a significantly higher incidence of cardiac disease than those without SCI (22% versus 4%, $p<0.05$), whereas no significant differences were noted in the incidence of the remaining risk factors between patients with and without SCI.

**Discussion**

MRI, the best method to detect organic changes in the brain, was used to detect SCI lesions in this study.
However, it is widely known that high signal intensity areas on T2-weighted MR images represent not only true infarctions but also other abnormalities, such as gliosis, cyst, demyelination, diverticulum, arterial venous ectasia, and vascular malformations.\textsuperscript{13-16} By using our criteria to exclude equivocal lesions, we attempted to select the infarctions as correctly as possible. However, there was a possibility of false detection of large Virchow-Robin spaces\textsuperscript{17} and old silent cerebral hemorrhage, which might not be distinguished from infarction with the use of such a low field strength of 0.1 T MRI.\textsuperscript{18}

The incidence of SCI in all subjects was 45 of 108 (42%). This incidence was similar to the results in a previous report\textsuperscript{4} that estimated lacunae according to almost the same criteria as in our study. The high incidence (62%) in the study of Lechner et al\textsuperscript{3} may have been due to diagnosis criteria differences; they counted all white matter lesions except caps and periventricular lines of hyperintensity only seen on T2 images.

The characteristics of the SCI lesions investigated in our study were very similar to those of other reports,\textsuperscript{1-5} that is, smaller than 1 cm, chiefly noted in the basal ganglia or white matter, and higher incidence in the right hemisphere. These characteristics suggest that the lack of symptoms with these lesions is related either to their small size and location in silent brain areas or to their production of only minor deficits that went undetected by the patients and physicians.

Hypertensive patients tended to have a higher incidence of SCI (47%) than normotensive subjects (33%). One reason for the lack of a significant difference in SCI incidence between the two groups was that many normotensive subjects had several other risk factors for stroke besides hypertension, so they were not healthy controls. We also studied SCI lesions in normotensive healthy volunteers in a preliminary study and found that the incidence of SCI in hypertensive patients (47%) was...
significantly higher than that of normotensive subjects (18%)\textsuperscript{19}.

The incidence of SCI increased significantly with age in hypertensive patients as compared with normotensive subjects. These results seem to be compatible with the results of Sadoshima et al\textsuperscript{20} that hypertension was the most important risk factor for progression of cerebral atherosclerosis.

The incidence of SCI in hypertensive patients was significantly higher in subjects with end-organ damage of the heart, kidney, or ocular fundi (arteriosclerotic change: S) than in those without such damage. This result shows that the progression of hypertensive changes in the brain is paralleled by that in other target organs and that assessment of each major organ in routine examination can predict latent damage in the brain. Although the existence of heart damage or arteriosclerotic changes of the ocular fundi due to hypertension in the 60s age group was closely correlated with SCI lesions, there was no correlation between the existence of other end-organ damage and the incidence of SCI in the 50s age group. This indicates that adequate management for the prevention of heart and retinal damage may have protected against the appearance of SCI lesions.

The average number of SCI lesions in hypertensive patients was significantly higher than in normotensive subjects. The significance of this was noted in each age decade and might indicate the effects of hypertension itself, excluding the age factor. The increased number of lesions in hypertensive patients reflected increased lesions in the area supplied by the perforating arteries, as shown in Figure 6. This result was compatible with the autopsy results of Fisher,\textsuperscript{21} in which the infarctions in hypertensive patients were multiple in the brain area supplied by perforating arteries, where hypertensive angioneurotic or arteriosclerotic changes were frequently observed.

This study shows that elderly hypertensive patients have SCI lesions with an unexpectedly high incidence when other hypertensive target organs were only moderately damaged. These lesions were the multiple small infarctions that chiefly appeared in the area supplied by perforating arteries. These results suggest that hypertension and progression of its organ damage strongly correlate with the appearance of SCI, especially in the area of perforating arteries. Conversely, assessment of hypertensive organ damage and protection against it by treatment can predict and protect against the early stage of brain damage and may be important in establishing methods to prevent brain infarcts.

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