Small Chronic Hemorrhages and Ischemic Lesions in Association With Spontaneous Intracerebral Hematomas

Akira Tanaka, MD; Yasushi Ueno, MD; Yoshiya Nakayama, MD; Kohichi Takano, MD; Shigeo Takebayashi, MD

Background and Purpose—It has been speculated that the same type of hypertensive small-artery disease can cause either intracerebral hemorrhages or ischemic lesions, depending on the circumstances.

Methods—To test this hypothesis, we examined the association between spontaneous intracerebral hematomas and both small chronic hemorrhages and ischemic lesions using echo planar and T2-weighted MRI. We considered a hypointense area to represent a hemorrhage and a hyperintense area to represent an ischemic lesion.

Results—We identified small hypointense lesions in 56.7% of 30 patients with intracerebral hematomas (mean age, 62.2 years; total number of lesions, 108) and in 25.4% of 59 patients without hematomas (mean age, 67.6 years; total lesions, 28). The incidence of hypertension was 88.3% in patients with intracerebral hematomas and 42.3% in those without. The hypointense lesions were found in 56.0% of 50 patients with hypertension, whereas they were found only in 10.3% of 39 patients without hypertension. The hypointense lesions were most common in the subcortex, followed by the putamen, pons, thalamus, and cerebellum. The hyperintense lesions were of a higher grade in patients with intracerebral hematomas than in those without. The hypointense lesions were commonly surrounded by hyperintense areas. Additionally, in 3 of 3 autopsied brains, we found hemosiderin deposits around arteriosclerotic microvessels and a surrounding small infarction in areas that had appeared as small hypointense lesions surrounded by hyperintensity on MRI. One specimen also had an organized miliary pseudoaneurysm.

Conclusions—Our findings indicate that spontaneous intracerebral hematomas are frequently associated with small chronic hemorrhages, ischemic lesions, and hypertension. We speculate that hypertensive intracerebral hemorrhage may have the same microangiopathic basis as cerebral infarction. (Stroke. 1999;30:1637-1642.)

Key Words: cerebral infarction ■ hypertension ■ intracerebral hemorrhage ■ magnetic resonance imaging

MRI, particularly T2*-weighted gradient-echo pulse sequences (echo planar imaging [EPI]), is highly sensitive to hemosiderin and thus is valuable for detecting chronic and small hemorrhages. Therefore, in 1996 we added the pulse sequence to routine MRI of the brain for patients with an intracerebral hematoma, a history of hypertension, or an age of >50 years.

On the other hand, it has been speculated that the same type of hypertensive small-artery disease can cause either intracerebral hemorrhages or ischemic lesions, depending on the circumstances. To test this hypothesis, we examined the correlation of both small chronic hemorrhages and ischemic lesions with spontaneous intracerebral hematomas on MRI. We also pathologically examined lesions that had been identified as small hemorrhages on MRI.

Methods

We divided the 89 subjects into 2 groups, depending on whether or not they had a spontaneous intracerebral hematoma. This diagnosis was defined as a hematoma with no identifiable underlying cause. The hematoma group consisted of 30 patients (19 men and 11 women) aged 43 to 77 years (mean ± SD, 62.2 ± 9.8 years). The hematomas were located as follows: putamen, 12; subcortex, 8; thalamus, 6; cerebellum, 3 and pons, 1. The nonhematoma group comprised 59 patients (35 men, 24 women) aged 46 to 91 years (mean ± SD, 67.6 ± 10.9 years), who had neurological deficits caused by lesions other than a spontaneous intracerebral hematoma.

MRI of the brain was obtained in these groups with 1.0-T scanners (Philips Gyroscan T10-NT) and included both axial T2-weighted (T2W) imaging (TR 3720 to 3730 ms, TE 90 ms, 90° flip angle, 3 excitations) fast spin-echo and axial T2*-weighted (TR 2178 to 2190 ms, TE 36 to 37 ms, 25° flip angle, 3 excitations) EPI. The studies were reviewed by 1 neuroradiologist and 2 neurosurgeons, whose consensus determined the MRI findings. The severity of a white-matter hypertensive area on T2W images was graded according to Fazekas and colleagues as follows: absent (grade 0), punctate foci (grade 1), beginning confluence of foci (grade 2), or large confluent areas (grade 3). Areas of ischemic parenchymal destruction (ie, lesions with an isointense signal and cerebrospinal fluid in their center) were categorized as lacunes (<10 mm in diameter) or infarcts according to Offenbacher et al. T2W images that showed signal loss...
in focal areas within the brain parenchyma were considered to indicate hemosiderin deposits unless CT scanning showed that these areas were calcifications. The majority of focal areas of signal loss consisted of homogeneous, round lesions 2 to 5 mm in diameter; we called these small hemorrhages.

We also determined whether our 89 subjects were hypertensive and evaluated the correlation between hypertension and MRI-defined lesions. Patients were considered hypertensive if they had a clinical history of hypertension, systolic pressure of >160 mm Hg, or diastolic pressure of >90 mm Hg, these being recorded on several occasions during a 1-week period.

Unpaired t tests were used to compare the incidence of hypertension and the incidence of hypointensities and hyperintensities on MRI between the patients with and those without intracerebral hematomas. The incidence of hypointensities and hyperintensities on MRI was also compared between the patients with and those without hypertension. The differences were considered to be significant at P<0.05.

In addition, we performed postmortem examinations of brain tissue from 3 patients whose MRI scans had shown small hypointense lesions surrounded by a hyperintense area. Case 1 was a 66-year-old woman without hypertension. Clinically, double vision, dysarthria, and dysphagia were evident. MRI scans showed abnormally enhanced lesions in the pituitary stalk and on the floor of the third ventricle and a hypointense lesion in the left corona radiata. She died of pneumonia 30 days after MRI examination. Autopsy showed a malignant lymphoma of B-cell type, which was infiltrating the optic chiasm, mamillary bodies and clivus. Case 2 was a 67-year-old man with hypertension. There had been progressive muscle weakness and atrophy in the extremities. MRI scans showed multiple hyperintense lesions and lacunes in the basal ganglia and a hypointense lesion in the left thalamus. He died of pneumonia 8 days after MRI examination. Autopsy showed an atrophic spinal cord, and a diagnosis of human T-lymphocytic virus I–associated myelopathy was made for the spinal cord lesion. Case 3 was a 50-year-old man with hypertension and hyperlipidemia. Clinically, bulbar signs and hemihypesthesia, right, were evident. MRI scans showed a hypointense lesion in the left side of medulla and a hypointense lesion in the right putamen. He suddenly died 2 days after MRI examination. Autopsy showed a subarachnoid hemorrhage caused by a rupture of the dissecting aneurysm in the right vertebral artery. Examination of brain specimens was undertaken to confirm that hypointense areas indicate foci of hemosiderin deposits from small chronic hemorrhages and that hypointense areas represent ischemic lesions. The brains were removed in toto and fixed in 10% formaldehyde solution for at least 3 weeks. Guided by the sagittal MRI localizing view, the fixed specimens were cut into 5-mm-thick axial slices. We carefully inspected these and chose from each patient at least 2 slices from areas that appeared hypointense on MRI and were unaffected by the primary disease process. These were stained with hematoxylin and eosin, Masson’s trichrome, and the Kluver Barrera technique for myelin before being examined microscopically.

Results

Table 1 shows the incidence of small hypointense lesions detected with EPI and T2W imaging as well as the incidence of hypertension in both groups. In the hematoma group, EPI showed a total of 108 small hypointense lesions in 17 patients: 3 patients had only 1 such lesion, 2 patients had 2 lesions each, 2 had 3 lesions, 4 had 4 lesions, and 1 patient each had 5, 7, 10, 14, 15, and 28 lesions. In the nonhematoma group, a total of 28 such lesions were found in 15 patients: 12 patients had a single lesion, 1 had 2 lesions, and 2 patients had 7 lesions each. The T2W images showed far fewer small hypointense lesions (a total of 39 for both groups compared with a total of 136 detected in both groups with EPI). The incidence of hypertension and small hypointense lesions on EPI or T2W imaging was significantly higher (P<0.01) in the hematoma group than in the nonhematoma group. Among the 136 small hypointense lesions, 54 (39.7%) were located in the subcortex, 38 (27.9%) in the putamen, 20 (14.7%) in the pons, 13 (9.6%) in the thalamus, and 11 (8.1%) in the cerebellum (Figure 1).

Table 1 also shows the hypointense lesions according to grade in both groups. The incidence of lacunes and hyperintense lesions of grade 3 was significantly higher (P<0.01, P<0.05) in the hematoma group, while the incidence of hyperintense lesions of grade 0 was significantly higher (P<0.01) in the nonhematoma group. The hypointense and hyperintense lesions were seen in the same locations. The hypointense lesions were commonly surrounded by a region of hyperintensity. Figures 2 and 3 show EPI or T2W images of 2 patients (1 with an intracerebral hemorrhage and 1 without).

Table 2 shows the incidence of small hypointense and hyperintense lesions detected with MRI in the patients with and without hypertension. The small hypointense lesions were found with EPI in 28 of 50 patients (56.0%) with hypertension and in 4 of 39 patients (10.3%) without hypertension. The difference was statistically significant (P<0.01). The patients with hypertension had hyperintense lesions of a higher grade and more lacunes than the patients without.

In the 3 autopsied brains, the small hypointense lesions were examined by serial sections, revealing the foci of old hemorrhages that had been caused by a rupture of arteriosclerotic microvessels measuring <200 μm in diameter, together with gliosis and incomplete ischemic necrosis in the sur-
rounding areas (in all of the cases). The old hemorrhages were identified as hemosiderin pigments within the perivascular space (in all of the cases) and as an organized pseudoaneurysm (in case 3; Figure 4).

**Discussion**

Clinical studies using CT scanning and pathological studies of the autopsied brain have found that systemic hypertension is closely associated with intracerebral hematomas and ischemic lesions such as lacunar infarcts or leukoaraiosis. The same type of hypertensive small-artery disease (i.e., involving parenchymal small arteries and arterioles) seems able to cause either intracerebral hemorrhages or ischemic lesions, depending on the circumstances. So-called fibrinoid change (necrosis) occurs in hypertensive small-artery disease, wherein the transendothelial transport of plasma proteins, including abundant fibrin and fibrinoid deposits, takes place within the vascular wall; thereafter, fibrosis occurs in which the fibrinoid material is replaced by collagen, a product of fibroblasts. If the wall of an artery or arteriole ruptures after such degeneration, blood clots adherent to the dissected vessels may form a pseudoaneurysm, which has also been called a “bleeding globe.” A bleeding globe is seen microscopically to consist of masses of red blood cells and platelets enclosed in concentric rings of fibrin. The fibrin serves as a sort of limiting membrane and tethers the globular body to the parent vessel, forming a small bead that might grossly suggest an aneurysm. A fibrin platelet formation of this type most likely represents the mechanism by which bleeding is brought to a halt. If the blood clots are resorbed and the layers of fibrin are replaced by layers of collagen, it is transformed into a “fibrous ball.” However, a study using electron microscopy found abrupt breakage of the arterial wall to be more common than microaneurysms at the sites of rupture in hypertensive intracerebral hemorrhages, where the surface is covered by polymerized fibrin with aggregated platelets. Furthermore, autopsy studies have found that hemosiderin-bearing macrophages are always deposited around the hemorrhages.

Although air, dense calcification, and acute hemorrhages produce similar signal changes on T2W MRI, hemosiderin deposits appear as areas of marked hypointensity. Because of its sensitivity for hemosiderin, MRI (particularly EPI)
useful for detecting chronic intracerebral hemorrhages.\textsuperscript{15,16} However, direct correlation between MRI and histopathologic findings has been needed to confirm that these hypointense lesions represent foci of hemosiderin deposits from petechial microhemorrhages.\textsuperscript{1}

Based on the MRI findings of hypointense lesions, a study of 120 patients with intracerebral hematomas found ischemic lesions such as white-matter hyperintensities, lacunes, or infarction in 68\% of cases and old hemorrhages, large or small, in 33\%.\textsuperscript{2} In another study, all 7 of the patients in whom MRI showed small chronic hemorrhages had also been chronically hypertensive.\textsuperscript{1} These small hemorrhages on MRI were located in the basal ganglia, thalamus, corona radiata, subcortical white matter, brain stem, and cerebellum, the same areas involved in lacunar infarction, cerebral hemorrhage, and leukoaraiosis. Also in autopsy studies,\textsuperscript{8 – 10} multiple small hemorrhages have been found within the brains of hypertensive subjects. Other studies\textsuperscript{17 – 19} have shown that punctate, early confluent, and confluent white-matter hyperintensities on MRI, respectively, reflect increasingly severe ischemic tissue damage caused by hypertensive microangiopathy. Similarly, hypertension, small hemorrhages, and ischemic lesions were all more common in our patients with intracerebral hemorrhages than in those without. Furthermore, the patients with hypertension had much smaller hemorrhages and more severe ischemic lesions than the patients without. The number of small hemorrhages in the patients with hematomas ranged from 1 to 28, and like the ischemic lesions, they were located in the subcortex, putamen, pons, thalamus, or cerebellum. Thus, our study confirmed that systemic hypertension is closely associated with both intracerebral hemorrhagic and ischemic lesions.

However, it is noteworthy that hypertension was absent in 16.7\% of 30 patients with intracerebral hematomas and small hemorrhages were present in 10.3\% of 39 patients without hypertension. Therefore, other factors besides hypertension must also be involved in the pathogenesis of cerebral microangiopathy and consequent hemorrhage. Furthermore, cerebral amyloid angiopathy can also cause such cerebral hemorrhages and/or infarctions.\textsuperscript{20,21} It commonly affects the small- and medium-sized vessels over the cortex or in the overlying leptomeninges of elderly patients. Consequently,

**TABLE 2. Incidence of Small Hypointensities and Hyperintensities on MRI in 89 Patients With and Without Hypertension**

<table>
<thead>
<tr>
<th>Group</th>
<th>Small Hypointensities</th>
<th>T2W Hyperintensity Grade</th>
<th>Lacune</th>
<th>Infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPI</td>
<td>T2W</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypertensive (n=50)*</td>
<td>28 (56.0)</td>
<td>17 (34.0)</td>
<td>5 (10.0)</td>
<td>24 (48.0)</td>
</tr>
<tr>
<td>Nonhypertensive (n=39)†</td>
<td>4 (10.3)†</td>
<td>1 (2.6)‡</td>
<td>20 (51.3)‡</td>
<td>14 (35.9)</td>
</tr>
</tbody>
</table>

Values are given as n (%).
*M/F, 29/21; mean±SD age, 65.2±10.7 y (range, 43–91 y).
†M/F, 25/14; mean±SD age, 66.9±11.0 y (range, 46–88 y).
‡Significantly different from hypertensive group (P<0.01).
Intracerebral hemorrhagic or ischemic lesions may occur in the cortex, usually sparing the subcortex, basal ganglia, cerebellum, and brain stem, and thus allowing differentiation from the lesions of hypertensive microangiopathy. Therefore, the histological material, which has such lesions in or near the cortex, should be further studied with Congo red staining and examined under polarized light to exclude cerebral amyloid angiopathy as a mechanism for both types of vascular lesions.

Some reports have proposed that intracerebral hemorrhage always requires an underlying ischemic lesion to set in motion the chain of events that ultimately shatters the surrounding brain, destroying the blood vessels that rupture and bleed.② Therefore, it has been argued③④ that focal brain ischemia may in some way lead to focal brain hemorrhage. In support of this contention, both our MRI and pathological examinations found small infarctions near the small chronic hemorrhages. Others⑤⑥ as well have identified small infarctions near small hemorrhages in microscopic sections from cadavers of patients who had hypertensive intracerebral hemorrhages.

In conclusion, spontaneous intracerebral hematomas are frequently associated with small chronic hemorrhages, ischemic lesions, and hypertension. We speculate that hypertensive intracerebral hemorrhage may have the same microangiopathic basis as cerebral infarction.

References


Figure 4. Pathological specimens from one of the autopsied cases (case 3: 50-year-old male with hypertension). An organized miliary pseudoaneurysm (arrows) is connected to an arteriosclerotic microvessel (A, hematoxylin and eosin [H&E], magnification ×200). Another microvessel is also markedly arteriosclerotic with fibrinoid changes (B, H&E, magnification ×280). A small infarction is evident where macrophages have accumulated and cystic changes have occurred around the pseudoaneurysm (C, H&E, magnification ×100). Hemosiderin pigments (arrows) contained within the macrophages are abundant around the arteriosclerotic microvessels (D, Berlin blue, magnification ×120).
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Stroke. 1999;30:1637-1642
doi: 10.1161/01.STR.30.8.1637
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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