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

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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 hemmorhages.\(^1,2\) 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.\(^3\) 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.
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 homogenous, 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, or had been taking antihypertensive medications. These were stained with hematoxylin and myelin before being examined microscopically.

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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 hypointense lesions of grade 3 was significantly higher ($P<0.01$) in the hematoma group than in the nonhematoma group. 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.
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 (ie, 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) is
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 and 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 hematomas 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,

\begin{table}[h]
\centering
\caption{Incidence of Small Hypointensities and Hyperintensities on MRI in 89 Patients With and Without Hypertension}
\begin{tabular}{lccccc}
\hline
\multicolumn{1}{c}{\textbf{Group}} & \textbf{Small Hypointensities} & \multicolumn{5}{c}{\textbf{T2W Hyperintensity Grade}} \\ 
& \textbf{EPI} & \textbf{T2W} & \textbf{0} & \textbf{1} & \textbf{2} & \textbf{3} \\
\hline
Hypertensive (n=50)* & 28 (56.0) & 17 (34.0) & 5 (10.0) & 24 (48.0) & 14 (28.0) & 7 (14.0) & 23 (46.0) & 1 (2.0) \\
Nonhypertensive (n=39)† & 4 (10.3)‡ & 1 (2.6)‡ & 20 (51.3)‡ & 14 (35.9) & 2 (5.1)‡ & 3 (7.7) & 5 (12.8)‡ & 0 \\
\hline
\end{tabular}
\begin{tablenotes}
\item Values are given as n (%).
\item *M/F, 29/21; mean±SD age, 65.2±10.7 y (range, 43–91 y).
\item †M/F, 25/14; mean±SD age, 66.9±11.0 y (range, 46–88 y).
\item ‡Significantly different from hypertensive group (P<0.01).
\end{tablenotes}
\end{table}
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.22 Therefore, it has been argued23,24 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. Others3,7 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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