Assessment of Lacunar Hemorrhage Associated With Hypertensive Stroke by Echo-Planar Gradient-Echo T2*-Weighted MRI

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Background and Purpose—Echo-planar gradient-echo T2*-weighted MR imaging (GRE-EPI) may detect hypointense lesions representing microhemorrhages with high sensitivity. The aim of this study was to evaluate the effectiveness of GRE-EPI for detecting old lacunar hemorrhages in hypertensive patients with stroke.

Methods—GRE-EPI was performed with a 1.5-T MRI system in 198 hypertensive patients with stroke (130 patients with hemorrhagic stroke and 68 patients with multiple lacunar stroke) and 66 age-matched healthy elderly individuals.

Results—Concomitant hypointense foci were found in 84 (66%) patients with hemorrhagic stroke, 46 (68%) patients with multiple lacunar stroke, and 3 (5%) healthy elderly individuals. These hypointense foci were noted in the lentiform nucleus in 61 (47%) patients with hemorrhagic stroke, in the caudate nucleus in 9 (7%) patients, in the thalamus in 54 (42%) patients, in the corticosubcortical region in 57 (44%) patients, in the brain stem in 40 (34%) patients, and in the cerebellum in 32 (25%) patients.

Conclusions—GRE-EPI is effective for the detection of lacunar hemorrhages induced by hypertension. (Stroke. 2000;31:1646-1650.)

Key Words: cerebral hemorrhage • echo-planar imaging • hypertension • lacunar infarction • magnetic resonance imaging

Lacunar hemorrhages are defined as small intraparenchymal hematomas that result from the extravasation of blood and are often clinically silent.1,2 Gradient-echo T2*-weighted imaging (GRE) can depict old lacunar hemorrhages as areas of sharply defined hypointensity.3–11 Hypertensive patients with spontaneous intracerebral hemorrhage are known to have concomitant silent foci of signal loss on GRE.3–11 Multifocal hypointense cerebral lesions on GRE are associated with long-standing chronic hypertension, advancing age, lacunar infarction, and extensive white matter lesions.8–11 Fazekas et al5 found multiple intracerebral foci of MR signal loss corresponding to focal hemosiderin deposits, with no evidence of other possible morphological abnormalities such as focal calcification or small vascular malformation, although the amount of hemosiderin deposition and the related field inhomogeneities were sometimes insufficient to be detected on GRE.5

Echo-planar imaging (EPI), in which an entire image is obtained from a single radiofrequency pulse excitation, has become a routine MR technique.12 An entire brain survey can be completed in as little as 2 seconds with the use of single-shot echo-planar gradient-echo T2*-weighted imaging (GRE-EPI). GRE-EPI has sensitivity comparable to GRE in the detection of chronic hemorrhage.13 GRE-EPI can visualize old lacunar hemorrhages as well-circumscribed areas of noticeable hypointensity. To our knowledge, however, there have been no large-scale studies on the prevalence and spatial distribution of old lacunar hemorrhages in hypertensive patients with stroke performed with GRE-EPI. The purpose of the present study was to detect foci of hypointensity in hypertensive patients with hemorrhagic or multiple lacunar stroke and to evaluate the effectiveness of GRE-EPI for the detection of old lacunar hemorrhages.

Subjects and Methods

Patients
From September 1997 to March 1999, we identified 198 consecutive Japanese hypertensive patients with either hemorrhagic stroke or multiple lacunar stroke who underwent both cranial CT and MRI including GRE-EPI at our hospital. Hypertension was defined by a history of increased blood pressure (>160/95 mm Hg) or medical treatment for hypertension. They were consecutively recruited by the review of radiological records.

The hemorrhagic stroke group consisted of 130 hypertensive patients (69 men and 61 women) aged 24 to 86 years (mean 64.0 years) with intracerebral hemorrhage that was proved by CT ob-
tained within 2 days after the onset. Patients with a known cause of hemorrhage such as trauma, cerebral tumor, coagulopathy, or vascular malformation were excluded. Putaminal hemorrhage was diagnosed in 48 patients, caudate hemorrhage in 2, thalamic hemorrhage in 40, subcortical hemorrhage in 20, brain stem hemorrhage in 6, and cerebellar hemorrhage in 14. The mean interval between the onset and MR examination was 6.3 days (range 0 to 28 days).

The multiple lacunar stroke group consisted of 68 hypertensive patients (45 men and 23 women) aged 55 to 88 years (mean 68.8 years) with multiple lacunar infarcts. Infarcts that involved the cerebral cortex or extensive areas of the subcortical white matter or that were >1.5 cm in greatest diameter were excluded. These patients all had 1 or more episodes of transient ischemic attack or lacunar stroke. CT revealed 2 or more focal hypodense lesions that were presumably of vascular origin and were unrelated to the index event.

The control group was 66 healthy elderly individuals (33 men and 33 women) aged 55 to 77 years (mean 62.1 years) who were consecutively recruited at annual health checks. They had normal blood pressure, no history of hypertension, and no evidence of neurological disorders.

Image Studies
MRI was performed with a 1.5-T superconducting unit (Magnetom Vision, Siemens) with a standard head coil to obtain axial fast spin-echo T2-weighted (FSE) images (repetition time [TR]/echo time [TE]/excitations, 3600/96/2). The slice thickness and gap were 5 mm and 1 mm, respectively. The imaging matrix and field of view (FOV) were 224×256 and 23 cm, respectively. Axial single-shot GRE-EPI (TE/excitations 25/1, flip angle 90°) were also obtained, with a slice thickness and gap of 5 mm and 1 mm, respectively. The imaging matrix and FOV were 128×128 and 23 cm, respectively. CT was performed with a Toshiba Xvigor scanner to obtain contiguous axial slices of 5 to 10 mm in thickness. The scanning was performed with the following parameters: 120 kV, 250 mA; matrix 512×512; and FOV 25 cm.

Criteria for Lacunar Hemorrhage on MRI
Hypointense foci were defined as lesions of more pronounced hypointensity on GRE-EPI when compared with FSE images. The corresponding areas were checked on CT, and areas with calcification were disregarded. In the patients with hemorrhagic stroke, lesions representing acute or subacute symptomatic hemorrhage were also excluded. These hypointense foci are presumed to be lacunar hemorrhages. Among the hypointense foci, the presence of a black ring was defined as a focus exhibiting a small hyperintense lesion inside the hypointense lesion on FSE images.

All scans were investigated independently by 2 experienced neuroradiologists, and the MR findings were considered by both to be definitely abnormal. The location of the lesions was ascertained, and they were grouped by cerebral regions as follows: lentiform nucleus, caudate nucleus, thalamus, corticosubcortical region, brain stem, and cerebellum.

Statistical Evaluation
A χ² test was used for comparison of the prevalence of hypointense foci between patients and control subjects. Nonparametric ANOVA with Bonferroni post hoc test was performed to compare the spatial distribution of hypointense foci between patients and controls.

Results
Concomitant hypointense foci were conspicuous on GRE-EPI and were frequent in the hypertensive patients with hemorrhagic stroke or multiple lacunar stroke (Figures 1 and 2). Black rings were detected on FSE images and were even more prominent on GRE-EPI (Figures 1, C and D). The prevalence and spatial distribution of concomitant hypointense foci including black rings are summarized in Tables 1 and 2, respectively.

Prevalence of Hypointense Foci
The numbers of concomitant hypointense foci are shown in Table 1. The number of hypointense foci was lower in the control group than in the hemorrhagic stroke group (P<0.001). A highly significant difference between controls and patients with multiple lacunar stroke was also shown (P<0.001). There was no significant difference between hemorrhagic and multiple lacunar stroke groups (P>0.1).

Spatial Distribution of Hypointense Foci
The numbers of the location of concomitant hypointense foci are shown in Table 2. There was no significant difference between hemorrhagic and multiple lacunar stroke groups (P>0.1).

Discussion
Lacunar hemorrhages, also known as type II lacunes, are defined as organized hemmorhages <1.5 cm in diameter.2 Lacunar hemorrhages occur at almost any site within the brain but show a predilection for the gray matter or the junction between the cortex and the white matter as well as the basal gray matter.1 Histologically, accumulation of hemosiderin-containing macrophages can be observed at sites of lacunar hemorrhage.14 Many of these hemorrhages are apparently asymptomatic.1

Although FSE is relatively less sensitive to the magnetic susceptibility effects of hemorrhage, GRE is sensitive to magnetic susceptibility effects and is commonly used for the detection of old lacunar hemorrhage.3–11 GRE-EPI requiring very short times for complete acquisition is also sensitive to the effects of the local static magnetic field inhomogeneities induced by the presence of hemosiderin.13 Furthermore, GRE-EPI can detect hyperacute intraparenchymal hemorrhage because susceptibility is increased by the paramagnetic effect of deoxyhemoglobin, which is the earliest observable hemoglobin breakdown product on MRI.18 Thus, GRE-EPI is thought to be highly sensitive for detecting hemoglobin degradation products.

Incidental foci of signal loss suggestive of past microbleeds have been associated with bleeding-prone microangiopathy.5 Histological examination of MR foci of signal loss has detected moderate to severe fibrohyalinosis, suggesting that lacunar hemorrhages are related to bleeding-prone microangiopathy.5 The principal cause of lacunar foci is long-standing hypertension; these lesions are not related to carotid disease, cerebral embolism, or diabetes mellitus.16 Lacunar infarction as well as intracerebral hemorrhage may be attributed to hypertensive small-vessel disease. Lipofibrohyalinosis is observed in small-vessel disease and is exacerbated by hypertension.17 It is generally postulated that a vascular lesion causes vessel wall fragility that can lead to intracerebral hemorrhage, but if rupture does not occur, segmental vessel occlusion subsequently evolves and produces lacunar infarction.17

Miliary aneurysms, known as Charcot-Bouchard aneurysms, occur in small arteries 100 to 300 µm in diameter and...
are seen as outpouchings of the vessel walls.\textsuperscript{17,18} Such aneurysms are rare in individuals $<$50 years of age and most commonly occur in the brains of hypertensive patients.\textsuperscript{17} Histological examination has shown that the walls of these aneurysms are fibrous and thin, lacking smooth muscle or an elastic lamina.\textsuperscript{17} Breaks in the elastic lamina, medial fibrosis, and intimal thickening are seen in many of the smaller arteries.\textsuperscript{17} Weakening of the walls of small blood vessels in patients with hypertension, particularly through the replacement of smooth muscle by fibrous tissue or by necrosis, may result in rupture of blood vessels with or without the prior formation of a microaneurysm.\textsuperscript{17} Small hemorrhages, hemo-

Figure 1. Small acute hemorrhage in left superior cerebellar peduncle in 76-year-old woman with multiple old lacunar hemorrhages. A, CT shows acute hemorrhage in left superior cerebellar peduncle. B, CT shows low-density areas in bilateral basal ganglia and thalami. Physiological calcification of bilateral globus pallidus is noted. C, FSE image shows black ring in left putamen (arrow). Multiple small hyperintense foci are noted in bilateral lentiform nuclei and right thalamus. D, GRE-EPI image reveals multiple hypointense foci in bilateral putamen and thalami. Symmetrical hypointensities of globus pallidus represent calcification.

Figure 2. Acute left putaminal hemorrhage in 65-year-old woman with multiple old lacunar hemorrhages. A, GRE-EPI image shows hypointense foci in brain stem and in right cerebellum near fourth ventricle. B, Fresh hematoma is noted in left putamen. Hypointense foci are identified in bilateral thalami and lentiform nuclei. C, Hypointense focus is seen in right frontal subcortical region.
Cerebral amyloid angiopathy occurs with aging and results in asymptomatic deposition of amyloid in the vascular walls. It commonly affects the cortical and leptomeningeal blood vessels while characteristically sparing the basal ganglia, thalamus, brain stem, and cerebellum. As cerebral amyloid angiopathy becomes advanced, there are structural changes to the walls of the amyloid-laden vessels, such as cracking between layers, microaneurysm formation, and fibrinoid necrosis. Spontaneous microbleeds have been histologically confirmed to correspond to focal areas of signal loss on gradient-echo T2-weighted MRI. Hypointensity foci in the corticosubcortical region may reflect spontaneous microhemorrhages induced by hypertensive microangiopathy, amyloid angiopathy, or both. However, we can easily suspect that clinically silent hypointense foci found in hypertensive patients generally should represent lacunar hemorrhages because concomitant hypointense foci found in hypertensive patients with stroke showed the same predilection for areas as symptomatic spontaneous intracerebral hemorrhages associated with hypertension.

In approximately 25% of patients with intracerebral hemorrhage or lacunar infarction, hypointense foci were visualized on GRE in the literature. Our study detected more foci representing lacunar hemorrhages in hypertensive patients with stroke as compared with previous studies that used GRE. There are 2 possible explanations for this observation. One is that lacunar hemorrhages, those affecting the central gray matter, are more common in Japanese patients with hypertension. An alternative explanation is that hemoglobin degradation products were detected by our more sensitive method of GRE-EPI. In 57% of Japanese patients with intracerebral hemorrhage, hypointense foci were detected on GRE-EPI. Although GRE-EPI is reported to have sensitivity comparable to the GRE in depicting chronic intracranial hemorrhage, further study of a side-by-side comparison of GRE-EPI with GRE in the same hypertensive patients would be warranted in this regard.

Tanaka et al reported that small chronic hemorrhages were relatively frequent in patients with intracerebral hematomas when compared with patients without hematomas, although approximately half of the patients without hematomas had hypertension. In the present study, the prevalence of lacunar hemorrhages in our hypertensive patients with stroke was far higher than in age-matched healthy individuals without a history of hypertension. Since no significant difference between the hemorrhagic stroke group and the multiple lacunar stroke group was shown in the prevalence or distribution of hypointense foci, it is indicated that lacunar hemorrhage apparently does not discriminate between major hemorrhagic or multiple lacunar stroke. These results strongly suggest that hypertension may induce lacunar hemorrhages as a result of small-vessel disease, leading to the occurrence of asymptomatic lacunar infarction or symptomatic intracerebral hemorrhage.

Recurrent hemorrhage occurs at a different location from the previous hemorrhage. Optimum antihypertensive therapy remains important to prevent recurrent bleeding, since poor control of hypertension increases the risk of recurrence. Therefore, GRE-EPI evidence of lacunar hemorrhage would seem to be a potential predictor for major hemorrhagic stroke.

In patients with lacunar infarcts, anticoagulant therapy is commonly used to prevent thrombosis. GRE-EPI, as a marker of clinically silent lacunar hemorrhage, should be tested in future studies, since GRE-EPI may provide useful information regarding the valid indications for anticoagulant therapy.

In conclusion, our data suggest that the use of GRE-EPI helps to better detect of small hypointense lesions representing lacunar hemorrhages, which are clinically silent and are common in hypertensive patients. Such lacunar hemorrhages may be a risk factor for spontaneous intracerebral hemorrhage, suggesting that GRE-EPI, with its ability to detect evidence of asymptomatic lacunar hemorrhage, should be added to the routine examination of hypertensive patients.

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References


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