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Multifocal Hypointense Cerebral Lesions on Gradient-Echo MR Are Associated with Chronic Hypertension

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PURPOSE: To investigate the basis for multifocal hypointense lesions within the brain as identified on T2*-weighted gradient-echo MR imaging in patients with no known or presumed cause of these lesions. **METHODS**: In the first of a two-part study design, we retrospectively reviewed a case series of 38 patients whose gradient-echo MR images showed multiple hypointense lesions within the brain parenchyma. Thirty-one cases in which the cause was known or presumed (eg, head trauma or cavernous angioma) were excluded from further review. The MR studies and clinical findings of the remaining seven cases were reexamined. In the second part, using a cohort study design with respect to hypertension, we prospectively reviewed the gradient-echo images from MR studies of 65 patients and control subjects enrolled in two ongoing clinical studies, one on "possible vascular dementia" (n = 33) and the other on "possible motor neuron disorder" (n = 32). **RESULTS**: In the first part of the study, we found seven cases with a pattern of multiple hypointense lesions involving the deep gray matter nuclei, especially the basal ganglia (n = 6) and thalamus (n = 5). In addition, involvement of the corona radiata (n = 5), brain stem (n = 4), and cerebellum (n = 3) was seen. Clinical review revealed a history of chronic hypertension in all seven patients. In the cohort study, we found three of 65 persons who had two or more focal hypointense lesions that involved the basal ganglia or thalami. Review of the clinical data showed that all three patients were being treated for hypertension; also, all three were patients from the "possible vascular dementia" group. **CONCLUSIONS**: The MR imaging pattern of multifocal hypointense lesions within the basal ganglia, thalamus, and other deep cerebral structures is more commonly found among patients with a history of chronic hypertension than in patients without chronic hypertension.

Index terms: Brain, magnetic resonance; Hypertension

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T2*-weighted gradient-echo magnetic resonance (MR) imaging is considered to be useful in the detection of lesions that contain substances that cause magnetic susceptibility effects, such as hemorrhage or calcification. It is helpful in the detection of small cavernous angiomas, hemorrhagic tumors, traumatic brain contusions, axonal shearing injuries, and hemorrhagic infarcts (1, 2). Several authors have recommended that the T2*-weighted gradient-echo pulse sequence be used routinely in conjunction with fast spin-echo pulse sequences because of the relative lack of sensitivity of fast spin-echo to magnetic susceptibility effects.

In everyday clinical practice, the T2*-weighted gradient-echo pulse sequence has been recommended for use in patients whose history suggests the likelihood of hemorrhagic lesions (such as head trauma) and in patients whose routine spin-echo images show hypointense foci suggesting one or more hemorrhagic lesions. Previously, we used the T2*-weighted gradient-echo pulse sequence to examine patients with cerebrovascular disease in whom the referring clinician and/or supervising radiologist

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believed it imperative to rule out occult hemorrhage. During the course of that work, we discovered seven patients who had multifocal hypointense lesions within the brain that were not attributable to a known cause. Because a review of the clinical and neuroimaging data of this case series indicated a possible correlation between the MR pattern and a history of chronic hypertension, we performed a retrospective cohort study to test the hypothesis that the finding of multiple hypointense lesions in the basal ganglia, thalamus, or corona radiata on gradient-echo MR images is associated with a history of hypertension.

Materials and Methods

Part I: Case Series

We reviewed the records of all MR studies of the brain performed between July 1992 and December 1994 in which $T2^*$-weighted gradient-echo MR images showed multiple hypointense lesions within the brain (n = 38). Most of these lesions had clinically determined causes (such as trauma-related axonal shearing injuries and cerebral contusions) or a radiologically diagnosed pathogenesis (such as cavernous angioma with a classic "popcorn" appearance of a hypointense rim around a hyperintense center on T2-weighted spin-echo MR images). In all, 31 cases had a known or presumed pathogenesis as determined by clinical history or typical radiologic appearance, including the following: multiple traumatic axonal shearing injuries and/or contusions (n = 13); multiple cavernous angiomas (n = 10); multiple hemorrhages related to arteriovenous malformation (n = 3); multiple hemorrhagic neoplasms (n = 2); surgery-related changes (n = 2); and multiple hemorrhagic infarcts (n = 1). These 31 cases were excluded from further consideration.

Seven cases remained in which no known underlying cause of the lesions could be identified. These patients consisted of four women and three men with a median age of 59 years (range, 49 to 77 years). The MR studies, computed tomographic (CT) scans, clinical history, and laboratory data of these seven patients were reviewed.

All the MR studies contained both axial T2-weighted fast spin-echo and axial $T2^*$-weighted gradient-echo pulse sequences. These studies had been performed with one of three 1.5-T MR units. The studies were rereviewed in a blinded fashion by two staff neuroradiologists, and the MR findings were determined by consensus. The scoring of hypointense lesions on both fast spin-echo and gradient-echo pulse sequences was performed by counting the lesions that were considered by both neuroradiologists to be definitely abnormal. The location of the lesions was ascertained, and they were grouped by cerebral regions as follows: brain stem, cerebellum, thalamus, basal ganglia, corona radiata, and the subcortical white matter. Lesions within the cerebral cortex were not formally counted because of the difficulty in separating true parenchymal hypointense lesions from adjacent pial blood vessels. The T2-weighted fast spin-echo images were interpreted before the T2-weighted gradient-echo images, because of the known greater sensitivity of gradient-echo images to magnetic susceptibility effects.

The $T2^*$-weighted gradient-echo pulse sequences had been obtained in the axial plane using the following parameters: 750–1000/25–40/2,4 (repetition time/echo time/excitations); a flip angle of 10°; a matrix of 256 × 128 or 192; a section thickness of 5 mm with a gap of 1.5 mm; and an imaging time of 3 to 6 minutes. The T2-weighted fast spin-echo sequences had been obtained in both axial and coronal planes using the following parameters: 2500–4000/92–110/1,2; an echo train length of 8; a matrix of 256 × 192; a section thickness of 5 mm with gap 1.5 mm; and an imaging time of 2 to 4 minutes.

CT scans were rereviewed in all seven patients to check for hemorrhage and calcification. The clinical history and laboratory data were obtained by chart review and discussion with the referring clinicians. As it became clear that hypertension was a common feature in all these patients, we formally directed our attention to systemic manifestations of hypertension, including cardiac, renal, and cerebrovascular symptoms and signs. The antihypertensive medication regimens were reviewed, and laboratory data such as electrocardiography, echocardiography, and blood urea nitrogen/creatinine values were studied.

Part II: Cohort Study

A prospective study group of 65 patients was derived from two research programs that required MR examinations for reasons other than those mandated by this study. Informed consent was obtained for participation in these studies. Group 1 consisted of 33 patients (15 women, 18 men) who were being examined for the effects of treatment of nimodipine for possible vascular dementia during the period 1993 to 1996. The median age was 78 years, with a range of 54 to 93 years. The standardized MR imaging protocol for these patients included proton density–weighted fast spin-echo, T2-weighted fast spin-echo, T1-weighted spin-echo, and $T2^*$-weighted gradient-echo images, all obtained in the axial plane. The pulse parameters were similar to those described above. Although these patients had two MR studies each, we selected the pretreatment MR study for review to rule out the possibility of any unknown effect from nimodipine treatment.

Group 2 consisted of 32 subjects (12 women, 20 men) who were being examined with an MR imaging protocol in addition to proton MR spectroscopy during the period 1995 to 1996. Twenty were being studied for "possible motor neuron disease" and the other 12 were healthy persons who had been selected as control subjects on the basis of two criteria: age of greater than 45 years and no history of neurologic disorders. The median age of these 32 subjects was 56 years, with a range of 41 to 76 years. The MR imaging protocol for group 2 included T2-weighted fast spin-echo and $T2^*$-weighted gradient-echo

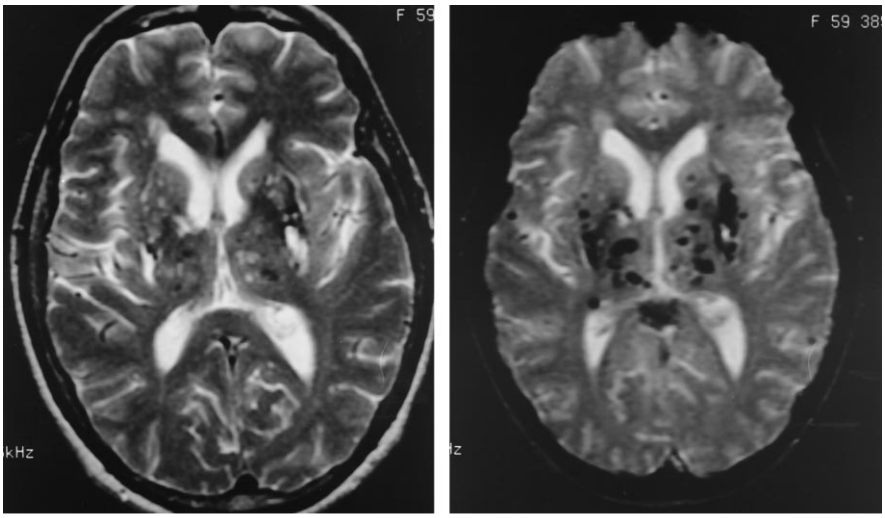

Fig 1. *A*, T2-weighted fast spin-echo MR image of a patient with chronic hypertension shows lacunar infarcts in both putamina posteriorly as well as a slitlike hypointense lesion in the anterior left putamen. Several small hypointense lesions are seen within the right basal ganglia and both thalami.

B, T2*-weighted gradient-echo MR image at the same level as *A* permits better visibility of a greater number of hypointense lesions within both basal ganglia and both thalami than seen on the T2-weighted fast spin-echo image.

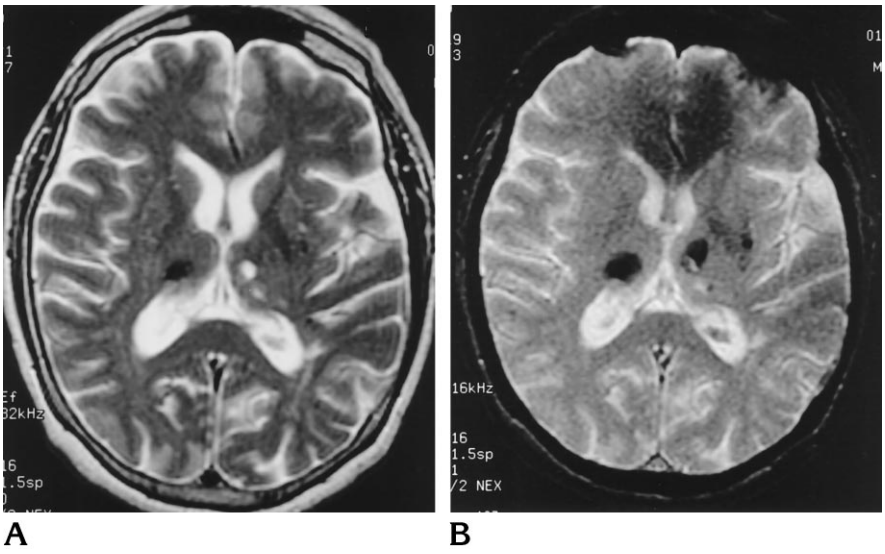

Fig 2. *A*, T2-weighted fast spin-echo MR image shows a hyperintense lesion within the left thalamus and a hypointense lesion within the right thalamus. A smaller hyperintense lesion is seen within the left thalamus. A small hypointense lesion is identified within the left putamen, but this is less visible than the thalamic lesions.

B, T2*-weighted gradient-echo MR image at the same level as *A* shows that the left thalamic lesions also contain hypointense components, suggestive of hemorrhagic lacunae. A hypointense lesion is clearly identified within the left basal ganglia as well.

images obtained in the axial plane with pulse parameters similar to those described in part I. Each patient had only one MR study that was obtained with this particular MR protocol at our institution.

The T2-weighted fast spin-echo and T2-weighted gradient-echo sequences from the combined 65 studies were reviewed as a group by two staff neuroradiologists blinded to the subjects' clinical status with respect to hypertension. The method of counting and scoring lesions was the same as described for part I; there was no overlap between these 65 patients and those studied previously. The clinical history had been obtained by the referring clinicians, and the presence or absence of chronic hypertension was ascertained by chart review for each of the 53 patients. The clinical history of the 12 control subjects had been obtained by interview. For the purposes of the cohort study, we defined the "chronic hypertension" group as those patients with known hypertension who had been or who continued to be treated with antihypertensive medication. Patients with untreated borderline hypertension were placed in the "no chronic hypertension" group.

Results

Part I

Retrospective consensus review of the MR findings indicated that the hypointense lesions predominantly involved the basal ganglia, thalamus, and corona radiata (Figs 1 and 2). Less frequent involvement of the brain stem, cerebellum, and subcortical white matter (including centrum semiovale and U-fibers) was noted (Table 1). Although hypointense foci were also noted in the cerebral cortex, formal separation

of pial blood vessels from intraparenchymal cortical lesions was difficult (Fig 3). Therefore, cortical foci were not counted formally. The gradient-echo pulse sequence permitted detection of many more hypointense lesions than the fast spin-echo pulse sequence did (Table 2). In particular, there were two instances (cases 5 and 6) in which gradient-echo sequences showed several hypointense lesions after fast spin-echo images failed to show such lesions.

Review of the CT scans obtained at the time of the MR studies revealed one case with a single punctate calcification in the left basal ganglion. One CT study showed several punctate densities in the right temporal subarachnoid spaces, thought to be residual deposits of myelographic contrast material. The remaining five studies showed no evidence of parenchymal calcifications, including in the thalamus and basal ganglia. Two patients had evidence of acute hemorrhage on CT scans obtained at the time of the MR studies. Two patients had follow-up CT scans after the MR examinations; one CT study showed a new acute hemorrhage in the left thalamus.

TABLE 1: Number of patients with hypointense lesions within specific structures on T2-weighted gradient-echo MR images (study 1; n = 7)

Basal ganglia	6
Thalamus	5
Corona radiata	5
Brain stem	4
Cerebellum	3
Subcortical white matter	3

Review of the clinical data established that all seven of these patients had a history of chronic hypertension, for which six patients were or had been on antihypertensive medication. Six patients had cardiac manifestations of hypertension, and two patients had slight elevations of blood urea nitrogen or creatinine levels, which potentially could be attributable to hypertension. However, none of these patients had had an episode of hypertensive encephalopathy. One patient did have uncontrolled hypertension associated with renal artery stenosis; the highest blood pressure recorded during that episode was 220/150 mm Hg, and no neurologic symptom or sign was reported at that time. All other patients had recorded peak systolic pressures at or below 200 mm Hg, and peak diastolic pressures at or below 110 mm Hg.

We did find that three patients each had one symptomatic episode of acute cerebral hemorrhage; in two cases, this was the basis for the MR studies, and in one case the episode was in the remote past, well before the MR examination. In addition, one patient had a new, symptomatic acute cerebral hemorrhage in the pos-

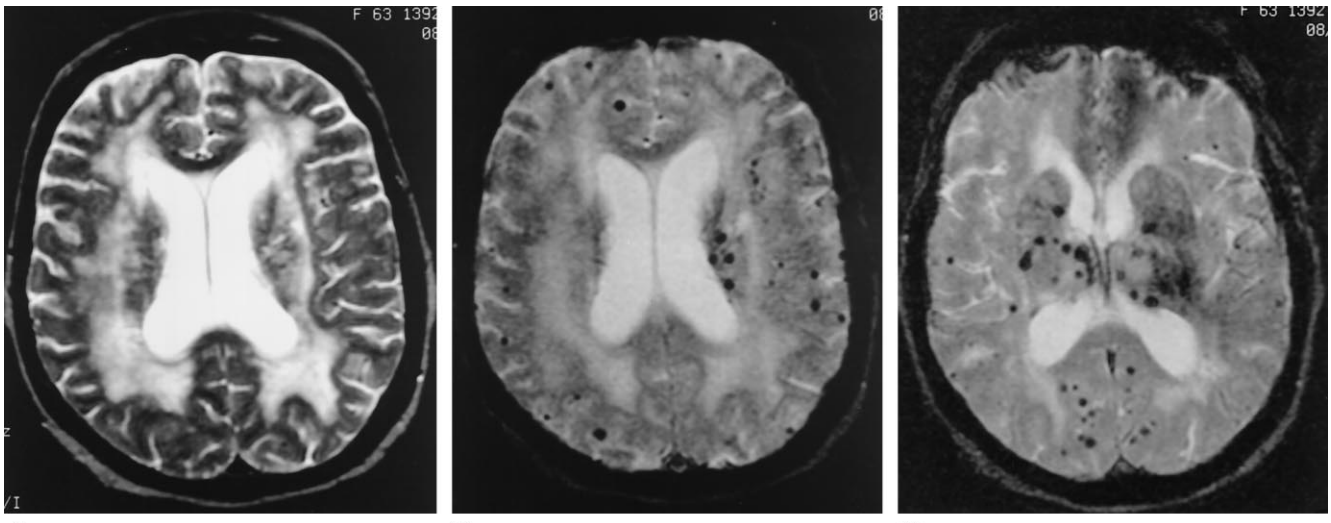

Fig 3. *A*, T2-weighted fast spin-echo MR image of a patient with chronic hypertension in whom progressively worsening dementia developed shows extensive white matter hyperintensity thought to represent severe leukoariosis. No hypointense lesion is identified clearly.

B, T2*-weighted gradient-echo MR image at the same level as *A* shows several hypointense lesions within the left corona radiata. Note cortical foci of hypointensity that could represent either cortical lesions or "blooming" of blood vessels within the cortical sulci.

C, T2*-weighted gradient-echo MR image shows multiple hypointense lesions within the basal ganglia and thalami bilaterally.

terior left thalamus 6 months after the MR study was performed (Fig 4). Three patients (two of whom overlap the acute hemorrhage group) had a history of stroke; two with a single episode each and one (case 7) with multiple strokes. In one patient, a brain biopsy (in the frontal lobe) was performed, the results of which showed evidence of leukoencephalopathy and vasculopathy most likely related to hypertension. No evidence of hemorrhage was found.

Part II

Of the 65 subjects in the cohort study, 27 had a history of chronic hypertension and 38 had no history of hypertension. Of the 33 subjects in group 1, 21 had a history of chronic hypertension treated by antihypertensive medication.

TABLE 2: Fast spin-echo versus gradient-echo MR imaging in the detection of intracerebral hypointense lesions (study 1)

Case	No. of Lesions Detected	
	Fast Spin-Echo Imaging	Gradient-Echo Imaging
1	2	5
2	12	56
3	14	44
4	2	10
5	0	4
6	0	6
7	1	3

Three of the 12 patients in the "no chronic hypertension" group actually had borderline hypertension, but none had been treated with medication. Of the 32 subjects in group 2, five had a history of chronic hypertension treated by antihypertensive medication. One of the 27 subjects in the "no chronic hypertension" group was reported to have borderline hypertension but had not been treated by medication. Of the five persons with hypertension, four were being examined for motor neuron disease and one was a control subject.

Prospective consensus review of the 65 patients revealed three in whom the gradient-echo images showed two or more hypointense foci in the basal ganglia or thalamus (Table 3). All three patients had a history of chronic hypertension. One case involved the basal ganglia bilaterally, one case involved the thalami bilaterally, and the third case involved the left thalamus and the pons. In none of the three patients had the lesions been detected on initial review of the T2-weighted fast spin-echo MR pulse sequence. Comparison with the clinical data revealed that these three patients came from group 1, the study group with "possible vascular dementia." Two were men, one was a woman; their ages were 69, 74, and 79 years, respectively. None of these patients had a history of significant head trauma or underlying neoplas-

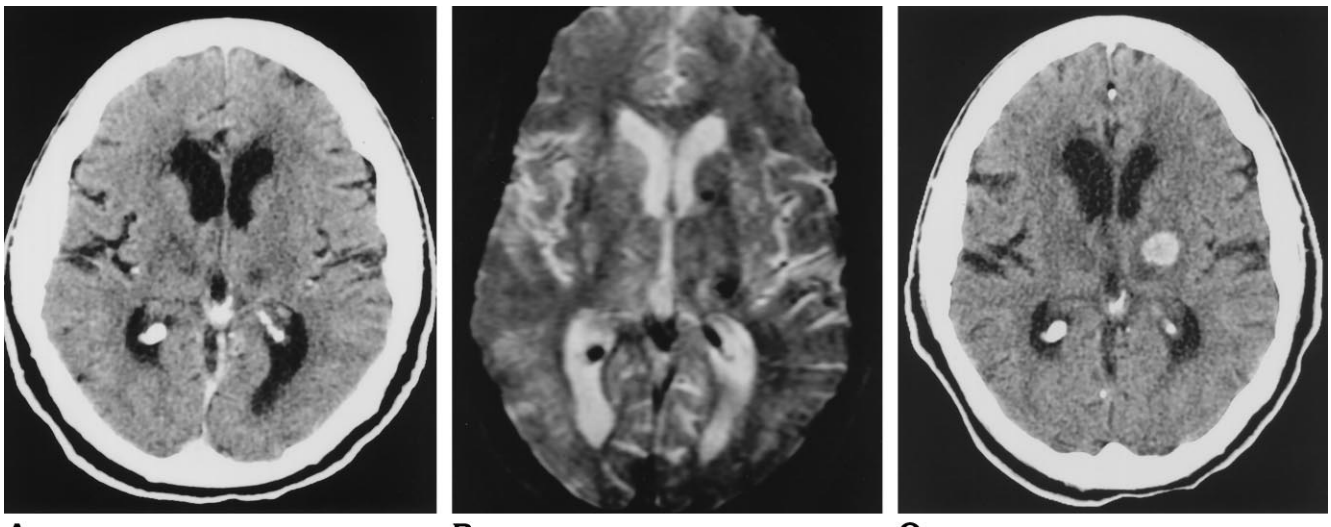

Fig 4. *A*, Axial CT scan of a patient with chronic hypertension and previous strokes indicates two lesions of decreased attenuation within the left and right thalamus, respectively. No evidence of acute hemorrhage is seen.

B, $T2^*$-weighted gradient-echo MR image obtained at the same time as the CT scan in *A* shows hypointense lesions within the left caudate head and the lateral aspect of the left thalamus.

C, Axial CT scan obtained 14 months after the MR study because of sudden onset of right leg weakness and left facial pain shows an acute parenchymal hemorrhage within the left thalamus.

TABLE 3: Retrospective cohort data from study 2

History of Chronic Hypertension	MR Pattern of Deep Cerebral Hypointense Lesions		
	Present	Absent	Total
Present	3	24	**27**
Absent	0	38	**38**
Total	**3**	**62**	**65**

Note.—Fisher's Exact Test shows that the association between the MR pattern of multifocal hypointense lesions and chronic hypertension has a *P* value of .07, suggesting a greater than 90% likelihood of nonrandom association.

tic disease. With respect to the association between chronic hypertension and this lesional MR pattern, statistical analysis by Fisher's Exact Test indicates that given one degree of freedom, the *P* value equals .07. Although the result does not exceed a 95% confidence interval, it indicates that there is approximately a 7% probability that chance alone would cause this difference in frequency of occurrence of this MR pattern between the "chronic hypertension" group and the "no chronic hypertension" group.

In two patients (both from group 1), cortical hemorrhagic infarcts were detected on both the T2-weighted fast spin-echo and $T2^*$-weighted gradient-echo pulse sequences. Neither patient had any other hypointense lesions detected on $T2^*$-weighted gradient-echo images of the remainder of the brain. Both patients had a history of remote cerebrovascular accident. One patient had a history of chronic hypertension and the other had a history of untreated borderline hypertension.

Discussion

The case series reports the observation of a pattern of multifocal hypointense lesions within the basal ganglia and thalamus on $T2^*$-weighted gradient-echo MR images. While these lesions have a predilection for the basal ganglia and the thalami, our initial case series indicated that they may also be seen within the corona radiata, brain stem, and cerebellum. The distribution of these hypointense lesions overlaps the same areas known to be involved by lacunar infarction (especially the basal ganglia and thalamus), cerebral hemorrhage (especially the basal ganglia and thalamus), and leukoariosis (especially the corona radiata). As lacunar infarcts and cerebral hemorrhage are often related to systemic hypertension, it was not considered surprising to find a history of hypertension among all seven patients with this MR pattern in our case series.

Because of the possible association between this MR pattern and chronic hypertension and the need to obtain data on control subjects (ie, patients without hypertension), we initiated a retrospective cohort study to compare the relative frequency of this MR pattern in patients with hypertension compared with those without hypertension. The reasons for pooling two different population sources were twofold. First, group 1 was presumed to be composed of many patients with chronic hypertension whereas group 2 was presumed to be composed of fewer patients with hypertension. Therefore, we included both population sources in order to obtain similar numbers of patients with and without hypertension. Second, we included both groups to maximize sample size. However, the sample size of 65 cases is still relatively small because of the low frequency of occurrence of this particular MR pattern (even among patients with hypertension).

The results of the cohort study indicated that the MR finding on $T2^*$-weighted gradient-echo images of multifocal hypointense lesions in the basal ganglia and/or thalamus is more common among patients with a history of chronic hypertension than in those without hypertension. In our cohort, three of 27 patients with chronic hypertension had this MR pattern whereas none of the 38 patients in the "no hypertension" group had this pattern on gradient-echo MR images. Although statistical analysis showed that this difference did not exceed the 95% level of significance, the results from this sample of 65 persons did exceed a 90% significance level. Therefore, a study of larger sample size (probably exceeding 100) is likely to have sufficient power to reach the 95% significance level.

The cerebral complications of chronic hypertension are most commonly described as parenchymal hemorrhage, lacunar infarction, and widespread leukoariosis (3). Parenchymal hemorrhage resulting from hypertension is usually associated with significant neurologic deficits, and radiologic signs of hemorrhage are easily found on either CT or MR studies. Concerning patients with cerebrovascular disease, the neuroimaging literature contains a large body of work related to areas of hyperintensity seen on T2-weighted spin-echo MR images (4,

5). However, only a few reports in the literature describe the presence of hypointense lesions within the brain in association with cerebrovascular disease, including associations with hemorrhagic lacunar infarction (6), amyloid angiopathy (7), and acute hypertensive encephalopathy (8). Both our case series and our cohort study demonstrated an association between multifocal hypointense lesions found on gradient-echo MR images and a history of chronic hypertension.

We recognize that the cohort study design does not prove that hypertension is the cause of the multiple hypointense lesions, nor does it eliminate the possibility that some other unknown confounding factor related to chronic hypertension—such as advanced age, cardiac disease, or some other clinical risk factor related to "possible vascular dementia"—is responsible for these lesions. However, the presence of multiple petechial microhemorrhages has been reported within the autopsied brains of persons with long-standing hypertension (9, 10). These microhemorrhages have been reported to occur at various sites in the brain, including the basal ganglia, thalami, and subcortical white matter; these are the same sites at which we have identified focal hypointense lesions on T2*-weighted gradient-echo MR images. Therefore, we believe it is reasonable to hypothesize that these hypointense lesions may represent foci of hemosiderin deposition from petechial microhemorrhages. Although pathologic correlation from the single brain biopsy sample in our case series does not substantiate our hypothesis, it is possible that microhemorrhage was not found in this case owing to sampling error on tissue biopsy. Further investigation, including direct MR-histopathologic correlation, is needed to test this hypothesis.

In summary, we have used T2*-weighted gradient-echo MR imaging to identify and determine the correlates of a pattern of multifocal hypointense lesions within the deep cerebral structures, especially the basal ganglia and thalami. The results of our cohort study suggest that this MR pattern is more common among patients with chronic hypertension than in those without hypertension. Obtaining T2*-weighted gradient-echo MR images in patients with cerebrovascular disease is likely to aid detection of cerebral lesions associated with hypertension.

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