Hypertensive Pontine Microhemorrhage

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Background and Purpose—This study investigated whether the topography of hypertensive pontine microhemorrhages (hPMHs) resembles that of larger primary pontine hemorrhages.

Methods—Sixty-nine consecutive patients with small-vessel disease underwent imaging with gradient-echo MRI, and 27 patients with hPMH were detected. Lesion size and location along the rostrocaudal (longitudinal), lateral (coronal), and anteroposterior (sagittal) axes were determined.

Results—A total of 52 hPMHs were identified in the 27 patients (mean, 1.93 ± 2.4 per patient). The lesions showed a nonrandom distribution, with a propensity to occur in the middle pons in the rostrocaudal axis, posterior half of the basis pontis in the anteroposterior axis, and central subdivision within the lateral axis. The area of hPMH ranged from 1.3 to 19.0 mm² (mean, 5.06 ± 3.72 mm²). The size of hPMH did not vary as a function of lesion location.

Conclusions—Previous studies reported that primary pontine hemorrhages tend to occur in the middle pons and at the junction of basis pontis and tegmentum. Therefore, topographical correspondences between large and small pontine hemorrhages may provide evidence that the 2 lesions share some etiological basis. Further investigation may determine whether hPMHs portend future symptomatic primary pontine hemorrhages. (Stroke. 2002;33:925-929.)

Key Words: dementia, vascular • intracranial hemorrhages • magnetic resonance imaging • small-vessel disease

Minute hemorrhages on gradient-echo MRI can result from various reasons, including hypertensive microangiopathy, head trauma, vascular malformation, hemorrhagic neoplasms, and cerebral amyloid angiopathy.1-2 Some studies suggested that microhemorrhage associated with hypertension could precede catastrophic intracranial hemorrhage (ICH).3-4 However, few studies have compared the anatomic distributions of large ICHs and microhemorrhages.

In this study, we investigated whether the topography of hypertensive pontine microhemorrhages (hPMHs) resembles that of large primary pontine hemorrhages (PPHs). Among the sites of predilection for hypertensive microhemorrhage, we specifically selected the pons because readily identified anatomic landmarks make lesion localization more reliable than at such sites as the basal ganglia and thalamus.

Subjects and Methods

Patients

Patients were recruited from the Memory Disorders Clinic at Samsung Medical Center in Seoul, Korea, between February 1999 and April 2000. The initial sample consisted of 69 consecutive patients who had focal neurological symptoms or signs of stroke and whose brain MRI scans showed lacunes or white matter ischemic changes in the absence of large territory infarction or ICH. From the initial cohort of 104 patients with focal neurological symptoms or signs of stroke, we excluded 35 patients for the following reasons: cortical or subcortical infarcts > 2 cm in diameter (n = 11), ICH (n = 3), no gradient-echo MRI because the MRI was taken before the visit (n = 11), and axial MRI not taken with the angle parallel to the anterior commissure-posterior commissure (AC-PC) line (n = 10). Because the patients were recruited from the dementia clinic, most patients (67 of 69) had dementia, which was confirmed by a neuropsychological test battery encompassing attention, language, praxis, visuospatial, memory, and frontal-executive functions. Thus, the cognitive impairment of the 67 patients, together with the focal neurological symptoms and signs, fulfilled the criteria for vascular dementia proposed by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).5 Scans from the 69 patients demonstrated only small-vessel changes (lacunes or white matter ischemic changes in the absence of large territory infarction or ICH). However, because MR angiography and conventional arteriography were not performed, we did not confirm whether the vascular pathology was confined to small vessels.6-7 All the patients did not have other potential causes of cerebral hemorrhage such as anticoagulant therapy, recent cranial trauma or surgery, or history of systemic neoplasm or scans consistent with vascular malformation.

The extent of signal hyperintensity on T2-weighted scans was assessed by 2 blinded investigators using a semiquantitative scale proposed by Scheltens et al.8 Briefly, the scale provides 4 sum scores: periventricular hyperintensities (score = 0 to 2 for each of the frontal cap, occipital cap, and bands; total score = 0 to 6), white matter hyperintensities (score = 0 to 6 for each of the frontal, parietal, temporal, and occipital areas; total score = 0 to 24), basal ganglia hyperintensities (score = 0 to 6 for each of the caudate nucleus, putamen, globus pallidus, thalamus, and internal capsule; total score = 0 to 30), and infratentorial foci of hyperintensities (score = 0 to 6 for each of the cerebellum, midbrain, pons, and medulla; total score = 0 to 24). To explore factors that might predict pontine microhemorrhage (ie, hPMH and nonhypertensive PMH) and micro-
Lesion Location

Lesion analysis was performed in the patients with hPMH (n = 69). Lesion Analysis

Method used for localization of hPMH. A, Axial gradient-echo MRI showing an hPMH. B, Magnified pontine area. Anterior-posterior location along the midsagittal line and lateral position along the coronal line were computed and then applied on the template as in Figure 3.

Imaging Technique of Gradient-Echo MRI

MR studies were performed with a 1.5-T MRI scanner (GE Signa). The T2*-weighted gradient-echo pulse sequences were obtained in the axial plane parallel to the AC-PC line with the following parameters: 284-ms repetition time; 20-ms echo time; 2 to 4 excitations; a flip angle of 20°; a matrix of 256 × 192; a 5-mm section thickness with a gap of 2 mm; and an imaging time of 1 minute 56 seconds.

Lesion Analysis

Lesion analysis was performed in the patients with hPMH (n = 27).

Lesion Location

Two neurologists who were blinded to clinical information agreed on the scan features signified the presence of microhemorrhages on gradient-echo MRI. Extrapontine microhemorrhages were classified according to their anatomic locations as brainstem (medulla or midbrain), cerebellum, basal ganglia, thalamus, or cortical.

All hPMHs were depicted on the templates provided by Schaltenbrand and Wahren.3 The axial plane of these templates and the axial MRI sections were obtained parallel to the AC-PC line. Investigators determined visually which MRI section best matched 1 of 3 pontine templates from the stereotaxic atlas. The slice numbers of these templates were 3, 12, and 20.5, corresponding to the upper, middle, and lower pons, respectively. In each section, we localized the hPMH according to the following anatomic references (Figure 1).

We determined the anteroposterior position along a midsagittal line extending from the anterior margin of the basis pontis to the anterior margin of fourth ventricle (ie, median sulcus). The lateral position of the hPMH was determined along a coronal line running through the hPMH and perpendicular to the line that defined the anteroposterior position. We scaled distances between the scans and the atlas by computing a percentage of distance along the midsagittal and coronal lines on the scan and applied these proportions to the corresponding template. After the microhemorrhage was depicted on the template with this method (Figure 2), the lesion location along the sagittal axis was classified into anterior third (ventral half of basis pontis), middle third (dorsal half of basis pontis), and posterior third (tegmentum). The boundary of the basis pontis and tegmentum was defined by the medial lemniscus. Likewise, along the coronal axis, the longest distance along the coronal axis first was divided into right and left pontine segment, and then each segment was divided into 3 equal segments with the lesion classification of lateral, middle, and medial subdivisions.

Lesion Size

In each slice, the lesion was visually identified and outlined with a manual pixelwise method with the aid of a PACS workstation (GE Medical Systems). The area of the lesion was computed in square millimeters.

Statistical Analysis

We used the χ² test to evaluate regional differences of hPMH along the 3 orthogonal axes and the nonparametric Kruskal-Wallis 1-way analysis of variance to compare lesion size between the axes. Right-left differences in sizes were also evaluated with the Kruskal-Wallis test. For comparison between PMH and non-PMH groups and between patients with and without microhemorrhage, we used the independent sample t test for continuous variables and the χ² test for categorical variables.

Results

Comparison of Clinical Features Between Patients With and Without PMH and Between Patients With and Without Microhemorrhage

The Table compares demographic variables, vascular risk factors, and ischemia severity on T2-weighted MRI between patients with
and without PMH and between patients with and without microhemorrhage. Patients with PMH (n=29; 2 without hypertension were included and 2 with cortical-subcortical hemorrhage were excluded) had a higher prevalence of hypertension than those without PMH (n=38). There was no significant difference between the PMH and the non-PMH groups with regard to the other factors. The total number of extrapontine microhemorrhages was significantly greater in the PMH than the non-PMH group. We also compared patients with (n=52) and without (n=15) microhemorrhage regardless of its location and found that the former group had more ischemic white matter signal change than the latter group. No significant difference was noted in other variables.

**Lesion Location**

The total number of hPMH lesions in the 27 patients was 52 (mean, 1.93±2.4 per patient). Lesion distribution along the rostrocaudal axis was not random, with 10 (19%) in the upper pons, 34 (65%) in the middle pons, and 8 (15%) in the lower pons (P=0.000). This regional difference in the distribution of hPMH may simply represent differences in the area of pons in each of the sections examined in this study. Therefore, we measured the cross-sectional area of slices from upper, middle, and lower pons in the 27 patients with hPMH and then calculated the density of hPMH (number of hPMH in each slice divided by the pontine area of the slice). Mean densities were 0.017 (10/576=0.017 mm²) in the upper pons, 0.5 (34/671=0.5 mm²) in the middle pons, and 0.013 (8/589=0.013 mm²) in the lower pons with significant regional differences (P<0.05). There was also a regional difference (P=0.000) along the coronal axis, with 30 of 52 (58%) occurring in the medial third, 21 of 52 (40%) in the middle third, and only 1 of 52 (2%) in the lateral third. Topographical

| Comparison of Demographic Variables, Vascular Risk Factors, and Ischemia Severity Between Patients With and Without PMH and Between Patients With and Without MH |
|-------------------|-------------------|--------|-------------------|-------------------|
|                  | PMH (+) (n=29)    | PMH (-) (n=38) | P      | MH (+) (n=52)    | MH (-) (n=15)    | P      |
| Sex, M/F         | 19/10             | 21/17            | ns     | 30/22             | 10/5             | ns     |
| Age, y           | 70.4±6.8          | 73.8±7.3         | ns     | 71.6±7.5          | 75.2±5.8         | ns     |
| MMSE score       | 17.5±6.7          | 17.8±6.8         | ns     | 17.6±6.3          | 18.2±8.4         | ns     |
| Hypertension, n (%) | 27 (93)          | 26 (68)          | 0.01   | 43 (82.4)         | 10 (66.7)        | ns     |
| Diabetes mellitus, n (%) | 6 (21)      | 14 (36)          | ns     | 15 (28.8)         | 5 (33.3)         | ns     |
| Hyperlipidemia, n (%) | 5 (17)          | 9 (23.6)         | ns     | 12 (23.1)         | 2 (13.3)         | ns     |
| Smoking, n (%)   | 12 (41)           | 10 (28)          | ns     | 19 (36.5)         | 3 (20.0)         | ns     |
| Ischemic heart disease, n (%) | 4 (13.7)      | 4 (10.5)         | ns     | 8 (15.4)          | 0 (0)            | ...    |
| Atrial fibrillation, n (%) | 0 (0)          | 0 (0)            | ns     | 0 (0)             | 0 (0)            | ...    |
| Current use of antiplatelet agent, n (%) | 15 (52)        | 12 (32)          | ns     | 21 (40.4)         | 6 (40.0)         | ns     |
| Extrapontine microhemorrhage, n | 561         | 215               | 0.00   | 776               | 0                | 0      |
| Cortex/BG/Thal/CBll/Midb/Med | 200/183/102/58/16/2 | 80/81/33/18/3/0 | (33/30/17/9/3/0.3) | 280/264/135/76/19/2 | (37/38/15/8/1.4/0) | (100/100/100/100/100) | 0      |

**Hyperintensity on MRI**

- Total 24.0±7.4 22.4±8.2 ns 24.9±7.3 16.8±6.5 0.00
- Infratentorial 2.1±1.8 1.8±2.3 ns 14.2±4.6 11.1±3.9 0.02
- Subcortical nuclei,† 9.3±4.8 7.1±8.0 ns 9.0±5.1 4.7±3.9 0.03
- Subcortical WM, n 13.2±4.5 13.7±4.6 ns 2.3±2.2 1.0±1.4 0.04

**Figure 3.** Topography of hPMH. hPMHs were depicted in the templates that correspond to upper pons (A), middle pons (B), and lower pons (C).
differences were also observed along the sagittal axis, with most lesions (45 of 52, 87%) in the basis pontis and only 7 of 52 (13%) in the tegmentum. Of hPMHs in the basis pontis, most (38 of 45, 84%) were located in the dorsal half. The number of right-sided PMHs (27 of 52) did not differ from that of left-sided PMHs (25 of 52) \( (P=0.851) \). The 27 patients with hPMH also had 540 extrapontine microhemorrhages that were distributed in the cortical regions \( (n=193) \), basal ganglia \( (n=179) \), thalamus \( (n=100) \), cerebellum \( (n=52) \), midbrain \( (n=14) \), and medulla \( (n=2) \).

**Lesion Size**

The area of the hPMH ranged from 1.3 to 19.0 mm\(^2\) (mean, 5.1±3.7 mm\(^2\)). There were no significant differences in size between lesions along the rostrocaudal axis (upper, 5.7±3.9 mm\(^2\); middle, 4.5±3.1 mm\(^2\); lower, 6.7±5.4 mm\(^2\); \( P=0.29 \) ), the anteroposterior axis (anterior third, 6.2±5.6 mm\(^2\); middle third, 4.6±3.2 mm\(^2\); posterior third, 5.9±2.7 mm\(^2\); \( P=0.42 \) ), or the coronal axis (lateral third, 4.0 mm\(^2\); middle third, 5.4±2.1 mm\(^2\); medial third, 4.9±4.1 mm\(^2\); \( P=0.70 \)). In addition, there was no difference in size between right-sided (5.6±4.5 mm\(^2\)) and left-sided (4.4±2.7 mm\(^2\)) lesions \( (P=0.25) \).

**Discussion**

Earlier studies reported that the prevalence of microhemorrhages was 6.4% in a healthy elderly population\(^{10} \) and up to 57% in patients with prior large cerebral hemorrhage\(^{1,11,12} \) or chronic hypertension.\(^{13} \) In our study, however, the prevalence of microhemorrhages was 78.2%. The prevalence of hPMHs (43.2%) was also higher than in previous studies (4% to 12%), even when microhemorrhages in other parts of the brainstem were included.\(^{1,4,13} \) The higher prevalence of microhemorrhage or PMH in our study may be explained, at least in part, by the higher prevalence of hypertension (53 of 67, 79%) in our sample compared with previous studies (41.5% to 63%).\(^{1,4,9,12,14} \) Also, the greater severity of small-vessel changes, defined through white matter signal abnormality, in our patients might have contributed to the higher prevalence of microhemorrhages and hPMHs. Although previous studies did not provide information about ischemia severity, small-vessel disease in our patients was severe enough to account for vascular dementia.

Earlier studies\(^{1,10,12} \) reported that the severity of white matter lesions was correlated with the frequency of microhemorrhages. The present study replicates those findings. Therefore, available data suggest that both white matter ischemia and microhemorrhages may result from common underlying microangiopathy associated with hypertension, thereby providing another explanation for the higher prevalence of microhemorrhage in our study.

We found that the distribution hPMH was not random. Specifically, lesions tended to occur in the middle pons along the rostrocaudal axis, central portion along the coronal axis, and dorsal half of basis pontis along the anteroposterior axis. Although the exact origin of hemorrhage in PPH is difficult to identify because of the small size of the pons and extension of hematoma into adjacent areas, Nakajima et al\(^{15} \) presented pathological evidence that the most frequent site of PPH is the middle pons. Other studies have shown that PPH occurs primarily at the junction of the tegmentum and basis pontis.\(^{14,16} \) Thus, these studies and our data document a topographical similarity between PMH and PPH.

The postulate that microhemorrhage may be etiologically related to ICH comes from various observations. First, hypertension is the most common cause of the microhemorrhages when other secondary causes (eg, head trauma) are excluded. Second, the predilection sites of microhemorrhages correspond closely with those of hypertensive large cerebral hemorrhage.\(^{4,12,13} \) Third, studies showed that patients with ICH had a higher frequency of microhemorrhages than those without ICH.\(^{3,4} \) Therefore, the topographical similarity between hPMH and PPH may provide another clue that primary microhemorrhages could predispose to ICH and that hPMH may be a risk factor for future symptomatic and potentially catastrophic PPH.

So far, we used the term “pontine microhemorrhage” and postulated that it is caused by hypertension. However, the term may be misleading because, although “cerebral hemorrhage” refers to bleeding into and consequent damage to brain tissue, the pathological substrate of “microhemorrhages” detected by MRI may be a deposition of hemosiderin in the perivascular space without parenchymal bleeding or damage.\(^{17} \) Also, it is not known whether the MRI-detectable pontine microhemorrhage represents a small “large pontine hemorrhage.” Therefore, although pontine microhemorrhage and large pontine hemorrhage may share risk factors and may to some extent colocalize, neither of these may necessarily imply a common underlying pathogenesis. The sample size in our study is small and limited to patients with vascular dementia associated with small-vessel disease. Thus, a study with a larger and less restricted patient group is needed in the future.

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**References**


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