Significance of Acute Multiple Brain Infarction on Diffusion-Weighted Imaging

Jae-Kyu Roh, MD, PhD; Dong-Wha Kang, MD; Seung-Hoon Lee, MD; Byung-Woo Yoon, MD, PhD; Kee-Hyun Chang, MD, PhD

Background and Purpose—Diffusion-weighted imaging (DWI) is superior to conventional MRI in identification of small new ischemic lesions and discrimination of recent infarcts from old ones. Thus, this technique is useful in the detection of acute multiple brain infarcts (AMBI). We sought to determine the frequency and the topographical and etiologic patterns of AMBI detected on DWI.

Methods—We studied 329 consecutive ischemic stroke patients who underwent DWI and MRI/MR angiography within 4 days of stroke onset. AMBI was defined as noncontiguous high signal intensities on DWI in 1 vascular territory. Stroke mechanism was determined according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST).

Results—We detected AMBI in 95 patients (28.9%). AMBI in anterior circulation was found in 62 cases: in 1 hemisphere in 42 (group A) and in bilateral hemispheres in 20 (group B). Twenty-two patients had AMBI in the posterior circulation (group C) and 11 in both anterior and posterior circulations (group D). The most frequent cause of stroke was large-artery atherosclerosis in groups A (33/42), B (9/20), and C (15/22) (P=0.02) and cardioembolism in group D (6/11) (P=0.02). Elevated fibrinogen or hematocrit was significantly associated with group B (P=0.01). In 9 patients in groups B and D, anatomic variations of anterior or posterior cerebral arteries or patent posterior communicating artery contributed to AMBI.

Conclusions—Different topographical patterns of AMBI are associated with different vascular pathologies and stroke mechanisms. Hemorheologic abnormality or vascular anatomic variations may be contributing factors in the pathogenesis of AMBI in bilateral cerebral hemispheres or in both anterior and posterior circulations. (Stroke. 2000;31:688-694.)

Key Words: cerebral infarction □ magnetic resonance imaging, diffusion-weighted □ rheology □ stroke, acute

Several studies have addressed the issue of multiple brain infarcts and attempted to correlate them with the underlying mechanisms and causes.1-5 However, the data on the frequency and etiology of multiple brain infarcts are still controversial, primarily because of differences in the methods used in the various studies. One important subgroup of multiple brain infarcts is composed of simultaneous infarcts. Bogousslavsky4 identified double infarcts in 1 cerebral hemisphere in 2% of the patients and acute multiple brain infarcts (AMBI) involving the anterior circulation in 5%,4 which were mostly caused by embolic mechanisms. Bernasconi et al1 reported the frequency of AMBI in the posterior circulation to be 11%. However, these data were mainly based on CT or MRI scans, and AMBI may be commonly overlooked when systematic MRI is not utilized. Furthermore, “silent” infarcts are not uncommon, and their frequency revealed by CT is reported to be 10% to 38%.6-8 Most silent infarcts were small and/or located in brain areas likely to leave the patient asymptomatic in the event of acute cerebral infarction,9 which may go undetected by conventional MRI.

Diffusion-weighted imaging (DWI) is sensitive to acute cellular injury in cerebral ischemia and can be used to detect ischemic lesions within the first few hours.10 The superiority of DWI relative to conventional MRI permits easier detection of small new ischemic lesions and differentiation of recent infarcts from old ones or nonspecific white matter high signal intensities.11-17 Thus, AMBI, which may be difficult to appreciate on conventional MRI, may be evident with DWI. Multiple brain infarcts on DWI have been recently studied, but the study considered old infarcts as well as recent ones.5 The purpose of our study was to determine the frequency and clinical, topographical, and etiologic patterns of AMBI detected on DWI.

Subjects and Methods
We considered 329 consecutive patients (209 males and 120 females; mean age, 62.3±10.9 years; age range, 16 to 88 years) with ischemic...
stroke who were admitted to our Stroke Unit from July 1997 to June 1999 and underwent both conventional MRI and DWI during the acute stage (within 4 days of stroke; the apparent diffusion coefficient was persistently reduced during this time window).15

Clinical Evaluation
All patients underwent systematic investigations, including complete blood cell count, blood chemistry, lipid profiles, coagulation abnormalities, urinalysis, chest roentgenogram, ECG, CT scan, MRI, and MR angiography. In selected patients, transthoracic and transesophageal echocardiography, including a microbubble test, transcranial Doppler, and catheter angiography, were also performed.

Risk factors included hypertension (blood pressure >160/90 mm Hg on 2 separate occasions), hypercholesterolemia (cholesterol concentration >6.216 mmol/L or LDL cholesterol >4.144 mmol/L), diabetes mellitus, regular cigarette smoking, myocardial ischemia, arrhythmia, valvular heart disease, a family history of stroke or ischemic heart disease, and a history of vascular disease or migraine.

The potential stroke mechanisms were determined according to the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST):18 (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-artery occlusion, (4) other determined etiologies, or (5) undetermined etiology.

The topography of infarcts was determined with reference to the maps establishing anatomic correspondence with dominant arterial territories proposed by Tatu et al.19,20 The diagnosis of AMBI was defined as multiple recent infarcts demonstrated on DWI. Infarcts had to include noncontiguous regions of abnormality on DWI that were present in >1 vascular territory. Uninterrupted lesions visible in contiguous territories were considered a single lesion and were excluded. The arterial territories were divided for the anterior circulation as follows: internal carotid artery (ICA), anterior cerebral artery (ACA), superior division of the middle cerebral artery (MCA), inferior division of the MCA, perforating branches of the MCA, medullary branches of the MCA, and anterior choroidal artery. The arterial territories for the posterior circulation were superficial posterior cerebral artery (PCA), perforating branch of PCA, basilar artery (BA), superior cerebellar artery (SCA), anterior inferior cerebellar artery (AICA), and posterior inferior cerebellar artery (PICA).

On the basis of the topographical patterns of AMBI, we divided patients into 4 categories: group A, patients with AMBI in 1 cerebral hemisphere in the anterior circulation; group B, patients with AMBI in the bilateral cerebral hemispheres in the anterior circulation; group C, patients with AMBI in the posterior circulation; and group D, patients with AMBI in both the anterior and posterior circulations.

MRI Evaluation
All patients underwent conventional MRI and DWI on a 1.5-T system with echo-planar imaging capability (Signa Horizon, Echo-speed; General Electric Medical Systems). Conventional MRI consisted of transverse T2-weighted sequences (repetition time [TR], 4000 ms; echo time [TE], 98 ms; 3 excitations) and sagittal T1-weighted sequences (TR, 450 ms; TE, 10 ms; 2 excitations) with 5-mm-thick slices. DWI was obtained in the transverse plane with a single-shot, echo-planar, spin-echo pulse sequence with TR of 6500 ms, TE of 107 ms, 1 excitation, and 2 b values (0 and 1000 s/mm²). The diffusion-gradient pulse duration was 31 ms, with a gradient separation of 33 ms and a gradient strength of 2.16 G/cm. Diffusion gradients were applied simultaneously along the 3 axes (x, y, z).

TABLE 1. Stroke Mechanisms in Patients With AMBI in 1 Hemisphere in Anterior Circulation

<table>
<thead>
<tr>
<th>Lesion Distribution</th>
<th>n</th>
<th>MCA</th>
<th>ICA</th>
<th>Aorta</th>
<th>CE</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial+superficial</td>
<td>5</td>
<td>...</td>
<td>3</td>
<td>...</td>
<td>1</td>
<td>1*</td>
</tr>
<tr>
<td>Superficial+deep</td>
<td>37</td>
<td>16</td>
<td>12</td>
<td>2</td>
<td>6</td>
<td>1*</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>16</td>
<td>15</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

LAA indicates large-artery atherosclerosis; CE, cardioembolism.

*Undetermined because of coexisting LAA and CE.
The criteria for the diagnosis of acute infarction on DWI included the following: (1) focal bright high signal intensities; (2) a location or configuration not thought to represent the normal anisotropy of diffusion; and (3) a location or configuration not thought to represent a magnetic susceptibility artifact (ie, typically seen near the interfaces between the brain and air-filled paranasal sinuses).

Results
Ninety-five (28.9%) of the total 329 patients had AMBI. Sixty-two of them were men, and 33 were women. Their mean age was 64.0 ± 10.0 years, ranging from 38 to 88 years.

Advantages of DWI
DWI was superior to conventional MRI in 43 patients (45.3%). DWI demonstrated additional ischemic lesions not seen on conventional MRI in 34 patients. Eighteen of these showed a single infarct on conventional MRI. DWI discriminated recent infarcts from old ones or nonspecific periventricular high signal intensities in 12 patients.

Frequency of AMBI
AMBI in the anterior circulation was found in 62 patients (28.8%) of 215 with anterior circulation ischemic strokes. Forty-two had AMBI in the unilateral hemisphere, and 20 had AMBI in the bilateral hemispheres. AMBI in the posterior circulation was found in 22 patients (21.4%) of the 103 with posterior circulation ischemic stroke. Eleven patients had AMBI in both the anterior and posterior circulations.

AMBI in 1 Cerebral Hemisphere in the Anterior Circulation (group A, n=42)
Five patients had superficial AMBI, involving the superior and inferior leptomeningeal territories of the MCA. Thirty-seven patients had superficial and deep AMBI. Twenty-five of these had AMBI involving the territories of the perforating and leptomeningeal branches of the MCA (Figure 1). Five patients had multiple border-zone (cortical and internal) infarcts. Seven patients had superficial MCA territory infarcts, 2 of which were associated with internal border-zone infarct, 2 with MCA perforator and internal border-zone infarct, 1 with ACA territory deep infarct, 1 with anterior choroidal infarct, and 1 with medullary branch infarct.

The potential cause of stroke was large-artery atherosclerosis in 33 patients (MCA disease [>50% stenosis or occlusion] in 16, ICA disease [>50% stenosis or occlusion] in 15, and aortic arch plaque in 2) and cardioembolism in 7 patients (Table 1).

Twenty-six patients had a first-ever stroke. All of these patients showed unilateral hemispheric symptoms or signs. Six patients had a lacunar infarct in the territory of the perforating branch of the MCA and additional infarcts in the territory of the superficial MCA. In 3 of these patients, the infarct located in the superficial territories was not evident on conventional MRI.

<table>
<thead>
<tr>
<th>Lesion Distribution</th>
<th>ICA</th>
<th>ICA + MCA</th>
<th>MCA</th>
<th>CE</th>
<th>SAO</th>
<th>Other or Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial+ deep</td>
<td>13</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>...</td>
<td>2</td>
</tr>
<tr>
<td>Deep+ deep</td>
<td>7</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>5</td>
<td>1*</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

SAO indicates small-artery occlusion. See Table 1 for definition of other abbreviations.

*Syphilitic vasculitis.

Figure 2. A 62-year-old male patient with advanced gastric cancer presented with left hemiparesis and Gerstmann syndrome. DWI shows acute multiple infarcts in the bilateral cerebral hemispheres (A and B). This patient had MCA occlusion on the right side.
AMBI in the Bilateral Cerebral Hemispheres in the Anterior Circulation (Group B, n=20)

In 13 patients AMBI involved the superficial and deep territories. It was associated with large-artery atherosclerosis in 8, cardioembolism in 3, and undetermined etiology in 2 of these patients. In 7 patients AMBI involved the bilateral deep territories. It was associated with small-artery occlusion in 5 of these patients, large-artery atherosclerosis in 1, and other determined etiology (syphilitic vasculitis) in 1 (Table 2).

Among 9 patients with large-artery atherosclerosis as a stroke mechanism, 4 had malignancy (gastrointestinal cancer in 3 and prostatic cancer in 1) (Figure 2), 7 had elevated fibrinogen level, and 1 had polycythemia (hematocrit >0.5). Among 5 patients with bilateral small-artery occlusion, 3 had elevated fibrinogen level and 1 had polycythemia.

Five patients had AMBI in the territories of the unilateral MCA and/or ACA and contralateral ACA. All of them had a common ACA trunk for the bilateral ACA territories (Figure 3). Three of these patients had carotid disease (unilateral in 1 and bilateral in 2), and the other 2 had cardiac sources of embolism.

Unilateral ICA or MCA disease was the only underlying vascular pathology in 2 patients. One of them with MCA disease had a malignancy (Figure 2), and the other with ICA disease had bilateral ACAs supplied by a common ACA trunk.

In 14 patients experiencing stroke for the first time, 8 presented with unilateral hemispheric symptoms or signs, while the other 6 showed bilateral hemispheric dysfunction.

AMBI in the Posterior Circulation (Group C, n=22)

AMBI involved the cerebellum and PCA territory in 6 patients; the brain stem and PCA territory in 4; the bilateral cerebellum in 4; the perforator zone and leptomeningeal branch of PCA in 3; the cerebellum, brain stem, and PCA territory in 2; the bilateral thalami in 2; and the cerebellum and brain stem in 1. The acute infarcts were most frequently located in the territory of the PCA (18 infarcts in the superficial PCA territory and 12 infarcts in the territory of the perforating branch of the PCA), followed by the PICA territory (n=16), the SCA territory (n=8), the AICA territory (n=5), and the territory of the perforating branch of the BA (n=3).

The stroke mechanism was large-artery atherosclerosis in 15 patients (vertebral artery disease in 6, BA disease in 4, PCA disease in 3, and PICA disease in 2 with bilateral PICA territory infarcts), cardioembolism in 6, and other determined etiology (stroke after catheter angiography) in 1 (Table 3).

Table 3. Potential Stroke Mechanisms in Each Group

<table>
<thead>
<tr>
<th>Stroke Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>LAA*</td>
</tr>
<tr>
<td>33 (78.6%)</td>
</tr>
<tr>
<td>20 (45%)</td>
</tr>
<tr>
<td>15 (68.2%)</td>
</tr>
<tr>
<td>11 (27.3%)</td>
</tr>
</tbody>
</table>

*More frequent in groups A, B, and C than in group D at P = 0.016 (Fisher's exact test).
†More frequent in group D than in groups A, B, and C at P = 0.017 (Fisher's exact test).
‡Exclusively found in group B at P = 0.0003 (Fisher's exact test).
AMBI in the Anterior and Posterior Circulations (Group D, n=11)

Six patients presented with posterior circulation stroke syndrome, 2 with anterior circulation stroke syndrome, and the other 3 with both anterior and posterior circulation stroke syndromes.

Cardioembolism was presumed to be the cause of stroke in 6 patients, large-artery atherosclerosis in 3, and other determined etiologies in 2 (stroke after catheter angiography in 1 and isolated central nervous system angiitis in the other) (Table 3).

The posterior communicating artery was patent in 3 patients: 2 with large-artery atherosclerosis and 1 with cardioembolism. Fetal-type PCA on the right side was evident in 1 patient (Figure 4) with AMBI in the temporoparietal and occipital lobes on the right side. A diffuse aortic arch plaque was presumed to be the source of the embolism.

Stroke Mechanisms According to Topographical Patterns

Large-artery atherosclerosis was the most frequent cause of stroke in groups A, B, and C (57/84) compared with group D (3/11) \( (P=0.016, \text{ Fisher’s exact test}) \) (Table 3). Cardioembolism was the most frequent in group D (6/11) compared with groups A, B, and C (16/84) \( (P=0.017, \text{ Fisher’s exact test}) \). Small-artery occlusion was exclusively associated with group B (5/20) compared with groups A, C, and D (0/75) \( (P=0.0003, \text{ Fisher’s exact test}) \).

Hemorheologic Abnormalities

Elevated fibrinogen or hematocrit levels were significantly associated with AMBI in the bilateral cerebral hemispheres in the anterior circulation. Thirteen patients (65%) in group B showed abnormal hemorheologic findings, while 25 of 75 patients (33.3%) with AMBI in other topographical distributions showed these same findings \( (P=0.02, \chi^2 \text{ test}) \). With the exception of patients with cardioembolism, the association remained significant \( (12/17 \text{ in group B versus } 18/56 \text{ in groups A, C, and D}) \) \( (P=0.01, \chi^2 \text{ test}) \).

Discussion

In our study AMBI detected on DWI represented >25% of ischemic strokes, which is higher than that of previous studies.\(^3\)\(^4\) The frequency of AMBI may have been underestimated before the era of DWI. The results from another recent study using DWI were different from ours; 19 (13.4%) of a total of 142 patients had acute multiple infarcts.\(^5\) The patients in their study underwent DWI within 15 days of stroke onset, and there is a possibility that DWI missed some of the acute ischemic lesions.\(^11\)

Our results suggest that MCA (38%) as well as ICA (36%) disease are the main causes of AMBI in 1 hemisphere in the anterior circulation. This finding is in contrast with the findings of Western studies, in which the prevalence of ICA stenosis or occlusion was approximately 75% in patients with double infarcts in 1 hemisphere,\(^1\) and ICA disease and cardioembolism explained approximately 60% of acute multiple infarctions in the anterior circulation.\(^4\) This discrepancy may be a result of a high prevalence of intracranial arterial disease in Asians.\(^21\) The topography of AMBI in 1 hemisphere in the anterior circulation was also different from the previous study.\(^1\) The most common topographical pattern in our study was superficial leptomeningeal and perforator zones of MCA (59.5%, 25/42), while Bogousslavsky\(^1\) reported the superior and inferior MCA leptomeningeal pattern to be the most common (approximately 50%). We believe that this difference also lies in the high prevalence of MCA disease in our patients. MCA disease might cause intra-arterial embolization to the distal MCA territory, even though it is unclear whether MCA perforator infarcts were due to thrombotic or intra-arterial embolic processes. In 3 patients who had a lacunar infarct in the territory of the perforating branch of the MCA, the superficially located infarcts on DWI were not evident on conventional MRI. This suggests that

Figure 4. An 82-year-old female patient with left homonymous hemianopia and left hemiparesis. DWI shows acute multiple infarcts in the territory of MCA (A) and PCA (B) on the right side. MR angiogram shows fetal-type PCA on the right side (C). This patient had diffuse plaques in the aortic arch.
these superficial infarcts were asymptomatic. In each of these patients, either the proximal ICA or the heart was the embolic source. This supports the hypothesis that local small-artery disease does not explain all small infarcts in the territory of the deep perforators.22,23

One third of the patients with AMBI in the anterior circulation had bilateral infarcts. Bogousslavsky et al4 found AMBI in the bilateral hemispheres in 25% of anterior circulation ischemic strokes that were associated with embolisms, usually arising from the heart. On the contrary, the main causes of stroke in this group in our study were large-artery atherosclerosis, followed by small-artery occlusion and cardioembolism. Small-artery occlusion was the main cause of bilateral deep cerebral infarcts.

It should be emphasized that bilateral or unilateral large-artery disease or small-artery occlusion may be associated with acute infarcts in both cerebral hemispheres. Although the factors that determine contemporary infarcts are unknown, we believe that hyperviscosity may be an important contributory factor. Grotta et al24 demonstrated a negative correlation between either hematocrit or serum fibrinogen levels and cerebral blood flow in stroke patients. Harrison et al25 found a direct correlation between elevated hematocrit levels and the size of cerebral infarction. An elevated hematocrit was also reported to be associated with the occurrence of watershed infarction distal to ICA occlusion.26,27 Elevated hematocrit or fibrinogen levels were significantly associated with bilateral cerebral infarction in patients with large-artery atherosclerosis or small-artery occlusion in this study.

Malignancy was exclusively associated with bilateral cerebral infarcts in our case series. A malignancy-associated hypercoagulable state may result from the production of coagulation promoters by the cancer.28 Atherosclerosis is not as common a cause of symptomatic cerebrovascular disease in patients with cancer as it is in the general population because severe atherosclerosis is less frequent in patients who die from cancer than in others.29 On the contrary, a retrospective analysis suggested that conventional large-artery atherosclerosis was the most common cause of cerebral ischemia in adult cancer patients.30 Although our patients with malignancy had severe large-artery disease, it seems likely that hypercoagulability may somehow contribute to multiple infarction in these patients.

We found AMBI in the posterior circulation in 21.4% of the cases of posterior circulation ischemic stroke, which is more frequent than the findings of a previous report.3 However, this discrepancy lies in the different interpretations of the definition of AMBI in the posterior circulation. We focused on the arterial trees, while Bernasconi et al3 emphasized topographical patterns and defined AMBI in the posterior circulation as the involvement of ≥2 of the 3 main sequential segments of the posterior circulation, as defined in the New England Medical Center classification.31,32 Thus, they classified infarction involving the superficial and deep PCA territory or bilateral infarcts in the thalamoperforate territory as a single lesion. Nonetheless, we found similar results in that embolisms from arterial or cardiac sources were the main etiologies of AMBI in the posterior circulation. In our study the most common locations of AMBI were the territories of the PCA, PICA, and SCA. Several other studies have shown that occlusion of the PCA, PICA, SCA, or distal BA is usually embolic, with in situ atherosclerotic disease being more uncommon.33–35

Approximately 10% of the patients in our study had multiple infarcts in both the anterior and posterior circulations, suggesting that the source of embolism was more proximal than the carotid arteries. In our study >50% of the patients in group D had a cardiac source of embolism. We found that the frequency of AMBI in the anterior and posterior circulations in our patients was lower than that in a previous Western study.4 This may be due to the lower incidence of cardiac-origin embolism in our country.36,37

On the other hand, ICA disease can cause simultaneous infarcts in the anterior circulation and PCA territory, because PCA may originate from the ICA (fetal-type of PCA) in up to 25% of cerebral hemispheres.38,39 Anterior circulation stroke may also be associated with steno-occlusive disease in the posterior circulation, because the posterior communicating artery is patent in nearly 67% of anatomic dissections.40 AMBI in the territories of both ACAs can also occur because a single artery supplies both medial aspects of the hemispheres in 18% of the normal population.41 Nine of the 31 patients in groups B and D in our study had multiple infarcts due to these kinds of anatomic variation.

This study contains a few limitations. First, simultaneity of multiple infarcts remains uncertain. Because we considered patients who underwent DWI within 4 days after stroke onset, we cannot exclude the possibility that multiple ischemic episodes occurred during this short period. Second, we did not consider other hemorheologic data, including factors V and VII, platelet aggregation and adhesion, or erythrocyte aggregation and flexibility.42

In conclusion, our findings emphasize the heterogeneity of the topographical and etiologic aspects of acute multiple brain infarction. Different topographical patterns are associated with different vascular pathologies and stroke mechanisms. DWI allows the identification of ischemic lesions that previously went undetected. This suggests that early identification of multiple infarcts with the use of DWI may provide early clues to stroke mechanism and guide therapeutic options in the acute phase of stroke.

References
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