Lesion Patterns and Stroke Mechanism in Atherosclerotic Middle Cerebral Artery Disease
Early Diffusion-Weighted Imaging Study

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Background and Purpose—Patterns and mechanisms of stroke in patients with atherosclerotic middle cerebral artery (MCA) disease remain unclear. We sought to identify lesion patterns and stroke mechanisms associated with MCA disease using early diffusion-weighted imaging (DWI).

Methods—We reviewed 185 acute ischemic stroke patients who had (1) symptomatic lesions located in the unilateral MCA territory on DWI performed within 48 hours of symptom onset, and (2) either corresponding MCA disease, internal carotid artery disease, or cardioembolism. Acute DWI lesion patterns were classified as (1) single (small perforator <2 cm; large perforator ≥2 cm; pial; large territorial; border-zone) and (2) multiple.

Results—MCA disease was diagnosed in 63 patients, 32 (50.8%) of whom showed multiple lesions. Concomitant perforator and pial infarcts (14/63, \(P < 0.001\)), concomitant perforator, pial, and border-zone infarcts (9/63, \(P < 0.001\)), and single small perforator infarcts (12/63, \(P = 0.001\)) were identified more often in patients with MCA disease than in those with cardioembolism or internal carotid artery disease. Small perforator infarcts were more common in patients with milder stenosis than with severe stenosis or occlusion of MCA (\(P < 0.001\)). Whether they occurred singly or in addition to other lesions, pial infarcts were identified more often in patients with severe stenosis or occlusion of MCA (\(P = 0.001\)).

Conclusions—Perforating artery infarcts, whether single or occurring in addition to pial or border-zone infarcts, are lesion patterns specific for MCA disease. This suggests that local branch occlusion and coexisting distal embolization may be a common stroke mechanism in patients with MCA disease. (Stroke. 2005;36:2583-2588.)

Key Words: magnetic resonance imaging ■ middle cerebral artery ■ stroke, acute ■ stroke classification
between November 1, 2002 and August 31, 2004. Stroke patients were identified by reviewing the registry, in which data had been prospectively collected. Patients were included in this study if they had (1) a final diagnosis of ischemic stroke with DWI confirmation of acute infarcts, (2) DWI performed within 48 hours of symptom onset, (3) ischemic lesions distributed within unilateral MCA territory or border-zone (BZ) areas, and (4) either corresponding MCA, ICA disease, or CE. We excluded patients who had (1) infarcts in multiple vascular territories beyond the unilateral MCA (eg, infarcts in both the MCA and the anterior cerebral artery, or bilateral hemispheric strokes), (2) stroke subtypes other than MCA disease, ICA disease, or CE, and (3) concomitant tandem ICA and MCA diseases. The time from onset was defined as the time patients were last known to be without new ischemic symptoms. This study was approved by the Institutional Review Boards of the Asian Medical Center. Patient informed consent was not obtained because the study was retrospectively designed.

MRI Assessments According to our protocol, ischemic stroke patients are scheduled to undergo first an emergent MRI scan and then a follow-up MRI scan 3 to 5 days after stroke onset. In patients who did not undergo emergent magnetic resonance angiography (MRA) because of logistic obstacles, the follow-up MRI protocol included an MRA scan. MRI examinations were performed with a 1.5 Tesla MR imaging unit (Signa, GE Medical Systems) with echo-planar capabilities. DWI was performed with a repetition time (TR) of 7500 ms, an echo time (TE) of 84 ms, a matrix number of 128x128, a slice thickness of 5 mm, an interslice gap of 2 mm, 20 axial slices, a field-of-view of 250 mm, and 2 b values of 0 and 1000 s/mm². A 3-dimensional time-of-flight intracranial MRA was performed with a TR of 25 ms and TE of 2 ms, and a 3-directional contrast-enhanced extracranial MRA from the aortic arch was obtained by means of an intravenous bolus injection of gadopentetate dimeglumine 20 mL (3 to 4 mL/s) with a TR of 6 ms and TE of 1 ms, with a flip angle of 20°, a matrix number of 512x512, and a field-of-view of 250 mm.

DWI lesion patterns were analyzed by an investigator (D.-W.K.) blinded to clinical and MRA data. The topography of ischemic lesions was determined using published templates. The vascular territories were divided into perforator, pial, and border-zone. Perforating artery infarct (PAI) included striatocapsular infarcts or perforating vessel infarcts of the MCA. Pial infarct (PI) was defined as an infarct occurring in the vascular territories supplied by the superior or inferior branches of the MCA. BZ infarcts were defined as anterior or posterior cortical BZ or internal BZ. Multiple DWI lesions referred to multiple noncontiguous hyperintense lesions occurring in more than 1 of the vascular territories described above. DWI lesions were categorized into 1 of the following 11 patterns (Table): single lesions ([1] small PAI (diameter <2 cm), [2] large PAI (diameter ≥2 cm), [3] PL, [4] large territorial infarct, or [5] BZ infarct) and multiple lesions ([6] PAI and PL, [7] PAI, PI, and BZ, [8] PAI and BZ, [9] PI and PL, and [10] PI and BZ, and [11] multiple BZ infarcts). MRA was independently reviewed by another investigator (D.W.K.), blinded to the clinical data and the DWI lesion patterns (except for side on which the lesion occurred). The degree of MCA stenosis was classified into 3 grades: moderate (signal reduction ≥50%), severe (focal signal loss with the presence of distal MCA signal), and occlusion.

Clinical Assessments Clinical data were obtained by reviewing stroke registry and medical records. In addition to MRI studies, all patients underwent complete blood count, erythrocyte sedimentation rate, blood chemistry, serologic testing, coagulation testing, ECG, chest radiography, and urinalysis. Transthoracic or transesophageal echocardiography and 24-hour ECG monitoring were performed on selected patients with a history of heart disease, clinical or radiological cardiac abnormalities, or abnormalities of cardiac rhythm on ECG; on those with no risk factors for atherosclerosis and age <45 years; on those with suspected infective or marantic endocarditis; and on those whose MRA results did not indicate an extracardiac source of stroke.

Association Between Ischemic Lesion Patterns and Stroke Subtypes

<table>
<thead>
<tr>
<th>Lesion Patterns</th>
<th>MCA Disease</th>
<th>ICA Disease</th>
<th>Cardioembolism</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Small PAI</td>
<td>12†</td>
<td>3</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>2. Large PAI</td>
<td>5</td>
<td>3</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>3. PI</td>
<td>6</td>
<td>6</td>
<td>27†</td>
<td>39</td>
</tr>
<tr>
<td>4. Large territorial</td>
<td>6</td>
<td>3</td>
<td>23†</td>
<td>32</td>
</tr>
<tr>
<td>5. BZ</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Multiple</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. PAI+PI</td>
<td>14*</td>
<td>1</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>7. PAI+PI+BF</td>
<td>9*</td>
<td>...</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>8. PAI+BF</td>
<td>2</td>
<td>1</td>
<td>...</td>
<td>3</td>
</tr>
<tr>
<td>9. PI+BF</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>10. PI+BF</td>
<td>4</td>
<td>13†</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>11. Multiple BF</td>
<td>1</td>
<td>1</td>
<td>...</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>38</td>
<td>84</td>
<td>185</td>
</tr>
</tbody>
</table>

*P<0.001; †P=0.001.

In patients with MCA disease, clinical symptoms were divided into lacunar syndrome (pure motor hemiparesis, pure sensory stroke, sensori-motor stroke, ataxic hemiparesis, dysarthria syndrome, dysarthria-clumsy hand syndrome) or nonlacunar syndrome, which was considered when cortical signs (aphasia, neglect, gaze deviation or altered consciousness) were present.

Stroke Subtype Classification MCA disease was diagnosed if there was a corresponding ipsilateral MCA stenosis ≥50% or occlusion on MRA at follow-up time point (3 to 5 days after onset), and if neither a cardiac nor a proximal arterial embolic source (eg, ICA) was identified. ICA disease was diagnosed if there was a significant ipsilateral ICA stenosis ≥50% or occlusion without evidence of MCA disease or cardioembolic sources. CE was diagnosed if embolicogenic heart disease defined according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) stroke classification criteria was identified in the absence of atherosclerotic diseases in corresponding cerebral vessels. Because the purpose of this study was to differentiate specific lesion patterns of MCA disease from those of ICA disease or CE, patients with a subcortical lesion with a proximal arterial disease or a cardioembolic source were classified as having proximal large artery disease or CE, respectively, regardless of lesion size. We also modified the criterion for size of lacune as less than 20 mm because the size of an acute infarct is usually larger on DWI than on CT or conventional MRI.

Data Analysis One of 11 DWI lesion patterns and 1 stroke subtype were determined in each patient. We evaluated the association of each DWI lesion pattern with the stroke subtype in a pair-wise fashion by applying Fisher exact test to each 2x2 table. A value of two-tailed P<0.05 was considered statistically significant. SPSS for Windows (version 11.5; SPSS Inc) was used for statistical analysis.

Results We identified 185 patients who met the eligibility criteria. There were 106 men and 79 women, and the median age was 67 years (mean±SD, 65.6±12.0 years; range, 15 to 89 years). MCA disease was diagnosed in 63 (34.1%) patients, ICA disease in 38 (20.5%), and CE in 84 (45.4%). Baseline
characteristics among 3 groups were comparable, except that ICA disease patients had more frequent diabetes (25.4% in MCA disease; 47.4% in ICA disease; 21.4% in CE; \( P=0.010 \)), and that CE patients had more severe stroke at onset (median National Institutes of Health Stroke Scale scores: 6 in MCA disease, 5 in ICA disease, and 9 in CE; \( P=0.015 \)).

The median time from onset to DWI scan was 8.5 hours (mean \( \pm \)SD, 13.8 \( \pm \)13.0 hours; range, 0.3 to 47.4 hours). DWI was performed within 24 hours of onset in 145 patients (78.4%). Both acute and repeated MRA scans were performed in 91 (49.2%) patients, MRA scan only at follow-up time point (3 to 5 days after onset) in 63 (34.1%), and acute MRA only in 31 (16.8%). The median time between initial and follow-up MRI/MRA was 3.7 days (mean \( \pm \)SD, 3.6 \( \pm \)1.3 days; range, 0.9 to 6.4 days). All patients diagnosed as having an MCA disease underwent either both acute and repeated MRA (n = 31) or MRA at follow-up time point (n = 32). In patients who had follow-up MRA, all MCA disease patients (n = 31) showed persistent MCA stenosis or occlusion on follow-up MRA, whereas CE patients with MCA occlusion on initial MRA (n = 31) showed significant or complete recanalization on follow-up MRA in most of cases (26/31, \( P<0.001 \)). Echocardiography was performed in 100 patients (54.1%), with both transthoracic and transesophageal echocardiography in 67 patients.

**Lesion Patterns and Stroke Subtypes**

The Table shows the association between DWI lesion patterns and stroke subtypes. Multiple DWI lesions were observed in 32 of 63 (50.8%) of the patients with MCA disease, in 21 of 38 (55.3%) of those with ICA disease, and in 21 of 84 (25.0%) of those with CE. Of the 63 patients with MCA disease, 16 exhibited moderate stenosis, 19, severe stenosis, and 28, occlusion.

DWI lesion patterns significantly associated with MCA disease as opposed to ICA disease or CE included concomitant PAI and PI (\( P<0.001 \), Figure 1A and 1B), concomitant PAI, PI, and BZ infarcts (\( P<0.001 \), Figure 1C), and a single small PAI (\( P=0.001 \), Figure 2). A single small PAI occurred more frequently in patients with moderate stenosis (9/16) than those with severe stenosis (3/19) or occlusion (0/28) (\( P<0.001 \)). Five single large PAIs were found only in patients with occlusion (\( P=0.037 \)). Whether occurring as a single lesion or concomitantly with other lesions, any PI (patterns 3, 6, 7, 9, 10) was more frequently observed in patients with severe stenosis or occlusion (ie, 3/16 in moderate stenosis, 15/19 in severe stenosis, and 17/28 in occlusion; \( P=0.001 \); Figure 3). However, there was no correlation between the degree of stenosis and any PAI pattern, any BZ infarct pattern, or any other lesion patterns.

On the other hand, concomitant PI and BZ infarct were associated with ICA disease (\( P<0.001 \); Figure 4A). Single Pls (\( P=0.001 \)) and large territorial infarcts (\( P=0.001 \); Figure 4B) were associated with CE.
Stroke Syndrome

In 63 patients with MCA disease, 31 (49.2%) patients showed clinical lacunar syndrome, and 15 (48.4%) of those had multiple DWI lesions. Of 31 patients with lacunar syndrome, 25 (80.6%) had the lesion involving perforating artery territory as a single small or large PAI (n=14) or a PAI plus additional lesions (n=11). Of the 42 patients with any PAI (patterns 1, 2, 6, 7, 8), those with large (≥2 cm) PAI lesion more frequently showed nonlacunar syndrome (14/23, 60.9%) than did those with a small (<2 cm) PAI (3/19, 15.8%; P=0.0045; Figure 5).

Discussion

We found that concomitant PAI and PI infarcts and concomitant PAI, PI, and BZ infarcts were associated with MCA disease more significantly than were ICA disease or CE. PI resulting from MCA disease may be the marker of embolism. Evidence of embolism in cortical branches from the thrombi generated in the MCA disease has been histopathologically documented.3,4 BZ infarcts may also be caused by embolism in a setting of hemodynamic compromise.15 Our findings thus suggest that the combination of local branch occlusion and embolism, with or without hemodynamic compromise, is a common pathogenesis of stroke resulting from MCA disease. The concept of coexisting multiple stroke mechanisms has previously been proposed.15 As postulated by Caplan and Hennerici, the combination of embolism and hypoperfusion can lead to impaired clearance of emboli and produce infarcts in BZ where perfusion is most impaired, especially in patients undergoing cardiac surgery16 or those with severe internal carotid stenosis.17 The coexistence of BZ infarcts and territorial infarcts was frequent in those studies.16,17 This idea is supported by our data in that 15 (83.3%) of 18 patients with BZ infarcts had concomitant PI or PAI. Our data also provide evidence that coexistence of multiple stroke mechanisms is a common pathogenesis of stroke in patients with MCA disease.

Single small PAI was the second most common lesion pattern in MCA disease in this study. The pathogenesis of this lesion may be attributed to one of the following mechanisms. The atheroma in MCA may occlude the origin of a perforating artery.18 Small embolic particles from MCA may lodge in a perforating artery.19 Lipohyalinosis in the perforating artery may cause classic lacunar infarcts independent of MCA disease. Single small PAIs were significantly associated with milder MCA disease rather than with severe stenosis or occlusion in our study. Although we assume that embolic mechanism is less likely in these cases because there were no concomitant pial territorial infarcts, the underlying pathogenesis of small PAI in MCA disease is unclear.

Figure 3. The difference in lesion patterns according to the degree of MCA stenosis in 63 patients with MCA disease.

Figure 4. A, PI+BZ pattern: a 62-year-old man presented with severe dysarthria and mild left hemiparesis. DWI shows pial territorial (thin arrows) and cortical BZ infarcts, and MRA shows focal stenosis of the right proximal internal carotid artery (thick arrow). B, Large territorial pattern: a 61-year-old woman presented with global aphasia and right hemiplegia. Acute MRI shows large left MCA territorial infarct on DWI, and left MCA occlusion (thick arrow) on MRA. Follow-up MRA shows complete recanalization of left MCA (thin arrow).
This study also showed that severe stenosis or occlusion of MCA was associated with any PI patterns. We suggest that patients with high-grade stenosis or occlusion of MCA have a higher risk of artery-to-artery embolization than those with milder stenosis. Wong and colleagues also showed that the number of microembolic signals on transcranial Doppler predicted the number of acute infarcts on DWI, which suggests that embolism is a common stroke mechanism in MCA disease. Pial infarcts accompanied by PAI were noted in patients with clinical lacunar syndrome (Figure 1B). This suggests that PIs may be clinically silent, because clinical lacunar symptoms correlated well with the PAI. However, it is unclear whether clinically silent PIs have occurred before or after or simultaneously with symptomatic PAI in these patients. Furthermore, whether those with high-grade MCA stenosis have a higher risk of early recurrent embolization and subsequent clinical events is unknown. Therefore, future studies using serial DWI/MRA and microembolic signal monitoring with long-term clinical follow-up will be needed to explore these issues.

In our study, 31 of 63 patients with MCA disease presented with clinical lacunar syndrome, and DWI revealed multiple lesions in 15 of those 31. The size of the PAI lesion may be related to the stroke syndrome. In our study, patients with a large PAI more frequently demonstrated nonlacunar syndrome than did those with a small PAI, regardless of concomitant additional lesions.

One of the advantages of this study is that either both acute and repeated MRA or MRA at follow-up time point was performed in all patients diagnosed as having an MCA disease. When intracranial arterial occlusion is observed at the acute stage of stroke, it would be difficult to differentiate atherosclerotic from embolic occlusion. Even when the results of cardiac evaluation are within the normal range, the possibility of CE cannot be completely excluded. In addition, performing intensive cardiac investigation in every stroke patient is not practical. In these regards, we suggest that repeated vascular investigation to monitor initially occluded vessels for recanalization may be useful in the diagnosis of atherosclerotic intracranial arterial disease. In this study, cardioembolic MCA occlusion showed frequent recanalization at follow-up MRA (Figure 4B), whereas atherosclerotic MCA occlusion showed persistent MCA steno-occlusion.

However, because some CE patients did not show recanalization at follow-up MRA, it is unclear whether atherosclerotic MCA disease was combined in these cases. The natural course of spontaneous recanalization according to stroke subtypes and the diagnostic utility of repeated vascular work-up need to be elucidated in the future.

This study has limitations, however. Although our stroke center has an organized clinical pathway for the diagnosis and management of stroke patients, the investigative work-up for stroke etiology was not identical in all patients. Echocardiography was not performed in all patients. MRA is less accurate than catheter angiography as a reference for vessel stenosis. Because pathologic studies were not performed in any of the subjects, our hypothesis of the stroke mechanism should be confirmed by autopsy.

In conclusion, our study shows that PAI, whether single or occurring in addition to pial or BZ infarcts, are lesion patterns specific for MCA disease. This suggests that local branch occlusion and coexisting distal embolization may be the most common stroke mechanism in patients with MCA disease.

Acknowledgments

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References

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