Association of Ischemic Lesion Patterns on Early Diffusion-Weighted Imaging With TOAST Stroke Subtypes

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Background: Different topographic patterns in patients who experience an acute ischemic stroke may be related to specific stroke causes.

Objective: To determine if lesion patterns on early diffusion-weighted imaging (DWI) are associated with stroke subtypes determined by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification.

Design: Cross-sectional study.

Setting: General community hospital.

Patients: We studied 172 consecutive ischemic stroke patients with a symptomatic lesion on DWI performed within 24 hours of stroke onset.

Main Outcome Measures: Lesion patterns on DWI were classified into single lesions (corticosubcortical, cortical, subcortical ≥15 mm, or subcortical <15 mm), scattered lesions in one vascular territory (small scattered lesions or confluent with additional lesions), and multiple lesions in multiple vascular territories (in the unilateral anterior circulation, in the posterior circulation, in bilateral anterior circulations, or in anterior and posterior circulations).

Results: We found an overall significant relationship between DWI lesion patterns and TOAST stroke subtypes (P < .001). Corticosubcortical single lesions (P = .01), multiple lesions in anterior and posterior circulations (P = .03), and multiple lesions in multiple cerebral circulations (P = .008) were associated with cardioembolism. Multiple lesions in the unilateral anterior circulation (P = .04) and small scattered lesions in one vascular territory (P = .06) were related to large-artery atherosclerosis. Nearly half (11/23) of the patients with a single subcortical lesion that was 15 mm or larger were classified as having cryptogenic strokes (P = .001), although 9 of these patients had a classic lacunar syndrome without cortical hypoperfusion.

Conclusions: Early DWI lesion patterns are associated with specific stroke causes. Conventional 15-mm criteria for lacunes, however, may underestimate the diagnosis of small-vessel occlusion with DWI.

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EARLY DIAGNOSIS of an ischemic stroke subtype may influence decisions about management, prognosis, and recurrence of stroke. The most widely used stroke subtype classification was devised for TOAST (the Trial of ORG 10172 in Acute Stroke Treatment).1 The TOAST classification of ischemic stroke subtype is based on clinical imaging features and ancillary diagnostic test results. Before the availability of diffusion-weighted imaging (DWI), the initial stroke classification in the early stage depended on clinical features, which are possibly misleading, and on baseline computed tomographic findings, which are often unrevealing. The initial impression of the stroke subtype has been estimated to be only 62% accurate when compared with assessment using all available clinical and diagnostic data at 3 months.2

Diffusion-weighted imaging is superior to other diagnostic modalities in the early detection of hyperacute stroke, small ischemic lesions, and multiple embolic strokes.3 When performed within 24 hours of hospital admission, DWI and magnetic resonance angiography substantially improve the accuracy of early diagnosis of stroke subtype.6 Various lesion patterns identified on DWI may have important clinical implications. There have been several studies addressing the correlation between ischemic lesion topography on DWI and stroke subtypes. Those studies, however, were limited to the specific stroke cause or pattern7-10 or considered only multiple ischemic lesions.11 None of the previous studies have addressed the question of whether specific ischemic lesion patterns on early DWI are associated with specific ischemic stroke causes.
METHODS

PATIENTS

This is a retrospective analysis of a natural history study of cerebrovascular disease approved by the Institutional Review Boards at the National Institute of Neurological Disorders and Stroke and Suburban Hospital, Bethesda. All patients gave written informed consent to participate in this study between January 1, 2000, and December 31, 2001. We included the patients with a final diagnosis of ischemic stroke who had an acute lesion corresponding to a clinical syndrome on DWI performed within 24 hours of stroke onset. A final diagnosis of ischemic stroke was made when patients presented with signs or symptoms of new-onset stroke lasting for 24 hours or longer or lasting for less than 24 hours but with magnetic resonance imaging evidence of acute stroke. The time from the onset of stroke was determined as the time the patients were last known to be without their new ischemic symptoms.

DWI ASSESSMENTS

Imaging was performed using a 1.5-T clinical magnetic resonance system. Diffusion-weighted imaging had the following variables: repetition/echo time, 6000/72 ms; 240-mm field of view; 128×128 matrix; 7-mm-thick axial-oblique slices aligned with the anterior and posterior commissures line; 20 slices contiguous, interleaved, and colocalized; and isotropically weighted images obtained with a b factor of 1000 s/mm².

Ischemic lesions on DWI were classified into single lesions (corticosubcortical lesion, cortical lesion, subcortical lesion with a diameter ≥15 mm, or subcortical lesion with a diameter <15 mm) (Figure 1), scattered lesions in 1 vascular territory (small [<15-mm] scattered lesions or confluent [≥15-mm] lesions with an additional lesion) (Figure 2), and multiple lesions in multiple vascular territories (in the unilateral anterior circulation, in the posterior circulation, in bilateral anterior circulations, or in anterior and posterior circulations) (Figure 2).

Multiple DWI lesions were defined as multiple noncontiguous hyperintense lesions in more than one vascular territory. The vascular territories were divided for the anterior circulation as the anterior cerebral artery, the middle cerebral artery (superior division, inferior division, and lenticulostriate), a single penetrating artery in the deep structure or white matter, the anterior choroidal artery, and watershed; in the posterior circulation, the circumferential branches of the basilar artery, cerebellar arteries (superior, inferior, and posterior inferior), and cerebellar watershed. The topography of ischemic lesions by vascular territory was determined with reference to published templates. Diffusion-weighted imaging lesion patterns were determined by consensus between 2 readers (D.-W.K. and J.A.C. or D.-W.K. and M.A.E.) blinded to clinical data, and a third reader’s (J.A.C. or M.A.E.) opinion was obtained in cases of disagreement.

STROKE SUBTYPE CLASSIFICATION

Stroke evaluation in our stroke center is based on a detailed clinical pathway algorithm. Routine evaluations for ischemic stroke included blood tests, urinalysis, chest radiographs, continuous electrocardiographic monitoring, transthoracic echocardiography, carotid ultrasonography, DWI, perfusion-weighted imaging, and intracranial magnetic resonance angiography. In selected patients, transesophageal echocardiography...
ography, including an agitated saline test, transcranial Doppler ultrasonography, extracranial magnetic resonance angiography, computed tomographic angiography, and digital subtraction angiography were performed.

The criteria of the TOAST classification were used to determine the stroke subtype: (1) large-artery atherosclerosis (LAA), (2) cardioembolism (CE), (3) small-vessel occlusion (SVO), (4) stroke of other determined cause, and (5) stroke of an undetermined cause, because 2 or more causes were identified, the stroke was cryptogenic, or there was an incomplete evaluation. The stroke subtype diagnosis was made based on the clinical, laboratory, and imaging data of initial and available follow-up studies. The criteria of infarct size for SVO were applied on DWI in the same manner as computed tomography or conventional magnetic resonance imaging. For example, if a patient with a cardioembolic source had a small (<15-mm) deep lesion on DWI but a large perfusion deficit, the patient was classified as having a CE. If a patient had a small deep lesion on initial DWI that enlarged (≥15 mm) on a follow-up DWI and no cause of stroke was identified, the patient was classified as having a cryptogenic stroke. However, the stroke subtype was determined blind to the DWI lesion patterns other than lesion size of the subcortical lesion for classification of SVO. The TOAST diagnosis made by one stroke neurologist (D.-W.K.) was compared with that described in the medical records. Discrepancies between those diagnoses were settled by consensus discussion with another stroke neurologist (J.A.C.).

STATISTICAL ANALYSIS

One DWI lesion pattern and one stroke subtype were determined in each patient. We evaluated the overall association of the 10 DWI lesion patterns with 7 stroke subtypes by Pearson χ² test with Monte Carlo approximation. We also evaluated the association of each DWI lesion pattern with stroke subtype in a pairwise fashion using the Fisher exact test.

Association of DWI Lesion Patterns With TOAST Stroke Subtypes

<table>
<thead>
<tr>
<th>Lesion Pattern</th>
<th>Total No.</th>
<th>LAA</th>
<th>CE</th>
<th>SVO</th>
<th>Other</th>
<th>2 Causes</th>
<th>Cryptogenic</th>
<th>Incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosubcortical</td>
<td>35</td>
<td>6</td>
<td>21*</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cortical</td>
<td>17</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Subcortical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15 mm</td>
<td>23</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11†</td>
<td>2</td>
</tr>
<tr>
<td>&lt;15 mm</td>
<td>29</td>
<td>0</td>
<td>3</td>
<td>17‡</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Scattered lesions in 1 vascular territory</td>
<td>14</td>
<td>5§</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Confluent and an additional lesion</td>
<td>10</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Multiple lesions in multiple vascular territories</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In 1 AC</td>
<td>13</td>
<td>5*</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>In the PC</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>In bilateral ACs</td>
<td>10</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>In the AC and the PC</td>
<td>16</td>
<td>1</td>
<td>11*</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>172</td>
<td>28</td>
<td>70</td>
<td>17</td>
<td>6</td>
<td>11</td>
<td>33</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: AC, anterior circulation; CE, cardioembolism; DWI, diffusion-weighted imaging; LAA, large-artery atherosclerosis; PC, posterior circulation; SVO, small-vessel occlusion; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*P<.05 by the Fisher exact test.
†P<.01 by the Fisher exact test.
‡P<.001 by the Fisher exact test.
§P=.06 by the Fisher exact test.

RESULTS

All patients from the clinical stroke registry during the study period (n=426) were considered. One hundred seventy-two patients met the inclusion criteria. There were 82 men and 90 women (mean±SD age, 73.9±13.6 years; age range, 21-101 years).

A single lesion was observed in 104 patients (60.5%), scattered lesions in one vascular territory in 24 (14.0%), and multiple lesions in multiple vascular territories in 44 (25.6%). Regarding stroke subtypes, CE was the most common, observed in 70 patients (40.7%), followed by LAA in 28 (16.3%), and SVO in 17 (9.9%). 2 or more causes identified in 11 (6.4%), an incomplete evaluation in 7 (4.1%), and other determined cause in 6 (3.5%).

In the Table showing the frequency of DWI lesion patterns and stroke subtypes, we found an overall significant association between DWI lesion patterns and stroke subtypes based on a 10×7 contingency table (χ²=162.5, P<.001).

Among 10 DWI lesion patterns, a single corticosubcortical lesion was associated with CE compared with other DWI lesion patterns (60.0% [21/35] vs 35.8% [49/137]; P=.01). Multiple lesions in anterior and posterior circulations (68.8% [11/16] vs 37.8% [39/156]; P=.03) and multiple lesions in multiple cerebral circulations (bilateral anterior circulations or anterior and posterior circulations) (65.4% [17/26] vs 36.3% [53/146]; P=.008) were also associated with CE. Confluent lesions with an additional lesion in one vascular territory tended to be related to CE (70.0% [7/10] vs 38.9% [63/162]; P=.09).

Patients with multiple lesions in the unilateral anterior circulation were more likely to have LAA (38.5% [5/13] vs 14.5% [23/159]; P=.04). Small scattered lesions in one vascular territory (35.7% [5/14] vs 14.6% [23/158]; P=.06) and multiple lesions in one cerebral circulation (the unilateral anterior circulation or the posterior circulation) (33.3% [6/18] vs 14.3% [22/154]; P=.08) tended to be associated with LAA.

In patients with a single subcortical lesion that was 15 mm or larger, 47.8% (11/23) were classified as having cryptogenic strokes (P=.001) because of the 15-mm criterion for SVO, although 9 of these 11 patients had a classic lacunar syndrome without cortical hypoperfusion on perfusion-weighted imaging. The cause of stroke was not identified in these patients.

In patients with a single subcortical small (<15 mm) lesion, the cause of stroke could not be explained by SVO in 41.4% (12/29). Seven patients had CE (n=3), cryptogenic stroke (n=3), or other determined cause (n=1); those patients had a corticosubcortical perfusion deficit, lesion expansion to 15 mm or more, or new additional lesions on follow-up DWI. Another 5 patients with clinical and radiological findings compatible with a lacunar infarct had additional cardiac or arterial sources of stroke.

COMMENT

We found acute ischemic lesion patterns on early DWI to be associated with specific stroke causes by the TOAST classification. Classifications of corticosubcortical single lesions and confluent lesions with an additional lesion in one vascular territory had associations with CE, while small scattered lesions in one vascular territory were associated with LAA. In addition, multiple lesions in anterior and posterior circulations or those in multiple ce-
rebral circulations were associated with CE, and multiple lesions in the unilateral anterior circulation were related to LAA, findings comparable to those of a previous study. These observations suggest that early DWI of acute stroke may provide information about stroke cause.

Arterial embolic stroke showed a smaller and more distal infarction than cardiogenic embolism in a comparison study between cardiac and arterial embolic stroke. Although we did not measure lesion volume, our findings support the concept that emboli from heart origin may be larger than those from proximal arterial origin.

The criteria for classification of vascular territories differ among studies. Some researchers regarded the whole middle cerebral artery territory as a single vascular territory, and others considered any separate scattered lesions in the brain as multiple lesions. This study, however, followed the same classification used by previous studies that focused on the frequency and cause of multiple infarcts.

Another important finding in this study was that nearly half (11 of 23) of the patients with a subcortical large (≥15-mm) lesion were classified as having a cryptogenic stroke because of the 15-mm TOAST criterion for SVO. Most of these patients (9 of 11) had a classic lacunar syndrome with no cortical perfusion deficits, no relevant angiographic abnormalities, and no evidence of embolic sources. The lesion diameter, however, was larger than 15 mm or larger, mostly ranging from 15 to 20 mm. Thus, we believe that those patients were misclassified as having a cryptogenic stroke because of the cutoff limit of size of lacunar infarct. Although a few studies selected a 20-mm diameter as the cutoff point of lacunes, most using DWI or conventional magnetic resonance imaging using the 15-mm criterion. The size cutoff of lacunes has been arbitrarily defined by convention on postmortem or long-term imaging measurements. Recently, the cutoff value of volume of lacunes corresponding to the value of diameter has been suggested. Nevertheless, it is still unclear which cutoff value of diameter should be accepted for the definition of SVO.

In patients with a subcortical small (<15-mm) lesion, 24.1% (7/29) were classified as having a stroke cause other than SVO because of a corticosubcortical perfusion deficit, lesion expansion, or new ischemic lesions on follow-up DWI. This result suggests that DWI alone may be unable to differentiate a lacunar infarct from a nonlacunar infarct. Perfusion-weighted imaging may provide additional information for an early accurate diagnosis of stroke cause, particularly in the patients with a small subcortical lesion.

This study has a limitation. Although our stroke center has a standardized protocol of diagnosis and management for stroke patients, the investigative workups for stroke patients could not be identical in all patients and could not be applied independent of DWI lesion pattern. The DWI also influenced the diagnosis of SVO, although DWI pattern did not otherwise influence the diagnosis of TOAST stroke subtype.

In conclusion, specific lesion patterns on acute DWI are associated with specific stroke causes. Identification of early DWI lesion patterns may provide early clues to stroke cause. However, the conventional TOAST criterion of lesion diameter for lacunar infarct may underestimate the diagnosis of SVO. Future prospective studies are needed to confirm these observations and to determine if DWI lesion patterns add independent information about stroke cause relative to the TOAST criteria.