Impact on Stroke Subtype Diagnosis of Early Diffusion-Weighted Magnetic Resonance Imaging and Magnetic Resonance Angiography

Lance J. Lee, MD; Chelsea S. Kidwell, MD; Jeffry Alger, PhD; Sidney Starkman, MD; Jeffrey L. Saver, MD

Background and Purpose—The purpose of the present study was to assess the diagnostic usefulness of early diffusion-weighted MRI (DWI) and MR angiography (MRA) in patients with ischemic stroke. Past approaches to stroke diagnosis required a series of diagnostic tests over several days of hospitalization. New magnetic resonance methodologies that include DWI and MRA may allow more rapid characterization of stroke pathophysiology. However, no previous study has assessed the impact on formal stroke subtype diagnosis of early imaging with DWI/MRA.

Methods—We analyzed 46 consecutive patients with acute ischemic stroke who underwent DWI/MRA within 24 hours of admission. Initial diagnoses were rendered with use of the 2 most widely used formal stroke subtype classification schemes, the TOAST and the Oxfordshire methods, which were applied to patients after CT/conventional MRI but before DWI/MRA. Modified TOAST and Oxfordshire diagnoses were then rendered based on the results of day 1 DWI, MRA, and DWI plus MRA. Final TOAST/Oxfordshire diagnoses at discharge were taken as the gold standard.

Results—Compared with final diagnoses, pre-MRI TOAST diagnoses matched final diagnoses in 48%, improving to 83% after DWI alone, 56% after MRA alone, and 94% after DWI plus MRA. For the TOAST diagnostic subtypes of large-vessel atherothromboembolism and small-vessel disease, pre-MRI diagnoses matched final diagnoses in 56% and 35% of patients, respectively, improving to 89% and 100% after DWI/MRA. Pre-MRI Oxfordshire diagnoses matched final diagnoses in 67% of patients, improving to 100% after DWI.

Conclusions—The use of DWI/MRA within 24 hours of hospitalization substantially improves the accuracy of the diagnosis of early ischemic stroke subtype. When initial management and clinical trial eligibility decisions are influenced by stroke subtype, day 1 multimodal MRI is advantageous as a guide to therapy. (Stroke. 2000;31:1081-1089.)

Key Words: angiography, magnetic resonance □ magnetic resonance imaging, diffusion-weighted □ stroke classification

The diagnosis of ischemic stroke subtype in the first few hours after hospital arrival has traditionally been performed through educated guesswork. Deductions regarding neuroanatomic localization, involved vascular territory, and etiologic vascular mechanism are reached on the basis of clues in the clinical history and the pattern of deficits on physical examination. The contribution of imaging has generally been confined to the exclusion of primary intracerebral hemorrhage with a negative early CT scan. This conventional approach has substantial accuracy limitations, even when formal stroke subtype classification criteria are used. For example, the TOAST trialists reported that initial subtype diagnoses matched final diagnoses in only 62% of cases. Other investigators have also found accuracy in the range of 50% to 70%.

Newer MRI techniques may assist early stroke subtype diagnosis. Diffusion-weighted MRI (DWI) can render ischemic fields visible within minutes of ischemia onset in animal models, and clinical studies have demonstrated the efficacy of DWI in humans in early visualization of the site and extent of ischemia. However, the impact of DWI findings on early ischemic stroke subtype diagnosis has not been systematically investigated. Magnetic resonance angiography (MRA) allows rapid characterization of the cervical and cephalic
large vessels. MRA detects and grades cervical internal carotid stenosis with an accuracy of 85% to 96% compared with digital subtraction angiography.16–21 With the use of MRA, stenoses and occlusions of intracranial vessels are identified with 80% to 100% sensitivity and specificity compared with catheter angiography.22–25 However, studies of MRA have generally been performed days after stroke occurrence rather than in the acute setting. In addition, prior investigations have generally focused on MRA/angiography correlations and have not systematically investigated the impact of MRA on stroke subtype diagnosis.

Together, DWI and cervical and cephalic MRA have the potential to identify the site of brain ischemia and the site of large-vessel disease within the first hours after stroke onset and hospital admission, providing detailed pathophysiological information that may improve the accuracy of stroke subtype diagnoses rendered in the acute phase. We therefore assessed the diagnostic usefulness of combined DWI and MRA within 24 hours of admission in acute ischemic stroke through the use of the 2 most widely used formal methods for stroke subtype classification: the TOAST and Oxfordshire classification criteria.

Subjects and Methods
The University of California Los Angeles Stroke Center Stroke Patient Registry was reviewed to identify all ischemic stroke patients who underwent intracranial MRA, extracranial MRA, and DWI imaging within 24 hours of admission between January 1, 1997, and March 31, 1998.

TABLE 1. Final Stroke Subtype Diagnosis and Initial (Before MRA/DWI) TOAST Stroke Subtype Diagnosis

<table>
<thead>
<tr>
<th>Initial Diagnosis (Before MRA/DWI)</th>
<th>Large Vessel</th>
<th>Cardiembolic</th>
<th>Small Vessel</th>
<th>Others</th>
<th>Unknown Cause</th>
<th>No. of Initial TOAST Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large vessel</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Cardiembolic</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Small vessel</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>3</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>5</td>
<td>23</td>
<td>1</td>
<td>8</td>
<td>46</td>
</tr>
</tbody>
</table>

Figure 1. Algorithm to render modified TOAST stroke subtype diagnosis, with MRA and DWI findings and clinical history and physical examination incorporated.
Ischemic stroke subtype diagnoses were rendered retrospectively at 5 possible time points: (1) immediately before DWI/MRA imaging (based on history, physical examination, and CT or conventional MRI studies), (2) immediately after DWI imaging (without MRA data), (3) immediately after MRA imaging (without DWI data), (4) immediately after combined DWI/MRA, and (5) at hospital discharge (final diagnosis).

MRI was performed with a 1.5-T Siemens Vision MR system equipped with echo planar imaging data acquisition capability designed to obtain rapid diffusion images. Diffusion imaging was performed with a slice thickness of 7 mm with no interslice gap and 2 levels of diffusion sensitization \( (b=0, 1000 \text{ s/mm}^2) \). The higher level of diffusion sensitization was replicated in each of the 3 orthogonal, principal gradient directions (read, slice select, phase encode \([X, Y, Z]\) planes), and DWI images were formed from the average of these. Extracranial MRA was performed with settings of TR 25, TE 9, flip angle 35°, images interpolated to 3.0-mm slice thickness, matrix \([192 \times 256]\), field of view 19, and superior saturation band. Intracranial MRA was performed with settings of TR 35, TE 7.2, flip angle 20°, images interpolated to 1.5-mm slice thickness, matrix \([200 \times 512]\), field of view 20, and superior saturation band. MRA images were processed with a maximum intensity projection, 3-dimensional time-of-flight technique. CT scans were obtained with 2 General Electric high-speed scanners with 5-mm slice thickness.

The TOAST classification method has 5 stroke subtype categories: (1) large-vessel atherothrombembolic, (2) cardioembolic, (3) small-vessel, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology.26 The Oxfordshire classification method contains 4 subtypes based on anatomic distribution of infarcts and corresponding clinical symptoms: (1) lacunar infarcts, (2) total anterior circulation infarcts, (3) partial anterior infarcts, and (4) posterior circulation infarcts.27 Pre-DWI/MRA diagnoses and final diagnoses were rendered according to the standard TOAST and Oxfordshire methods.26,27 For the DWI and post-MRA TOAST diagnoses, we created modified TOAST classification criteria that incorporate MRA alone, DWI alone, and MRA\(_1\)DWI. For the post-DWI Oxfordshire diagnoses, we created modified Oxfordshire classification criteria that incorporate DWI.

The modified TOAST classification differs from the original in the following ways: (1) vascular imaging by MRA was permitted to influence diagnosis in the same manner as carotid duplex, (2) DWI imaging of infarct size, location, and topography was permitted to influence diagnosis in the same manner as CT or conventional MRI of infarct size, location, and topography, and (3) if there was a conflict between history/physical examination findings and imaging findings, imaging findings were accepted as decisive (eg, a patient with a nonclassic lacunar clinical syndrome but a small, deep infarct on DWI and no large-vessel stenosis on MRA was classified as having a small-vessel stroke). To make application of the complex TOAST diagnostic method more uniform, we created formal algorithmic decision trees to guide diagnostic assignment (Figure 1 and supplemental figure1). The modified Oxfordshire classification differs from the original in 2 ways: (1) it incorporates DWI or other parenchymal imaging findings, and (2) if there was a conflict between history/physical examination findings and imaging findings,

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**TABLE 2. Final Stroke Subtype Diagnosis and TOAST Stroke Subtype Diagnosis After MRA/DWI**

<table>
<thead>
<tr>
<th>Initial Diagnosis (After MRA/DWI)</th>
<th>Final Discharge Diagnosis</th>
<th>No. of TOAST Diagnoses After MRA/DWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large vessel</td>
<td>Small vessel</td>
<td>Unknown cause</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>Cardioembolic</td>
<td>Cardioembolic</td>
</tr>
<tr>
<td>Small vessel</td>
<td>Cardioembolic</td>
<td>Cardioembolic</td>
</tr>
<tr>
<td>Others</td>
<td>Cardioembolic</td>
<td>Cardioembolic</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>Cardioembolic</td>
<td>Cardioembolic</td>
</tr>
<tr>
<td>Total</td>
<td>Cardioembolic</td>
<td>Cardioembolic</td>
</tr>
</tbody>
</table>

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imaging findings were accepted as decisive (eg, a patient with a nonclassic lacunar clinical syndrome but a small, deep infarct on DWI was classified as “lacunar infarct-LACI”).

To guide early diagnoses, in addition to CT and conventional MRI, results were available for all patients from chart medical histories and physical examinations, ECGs, chest radiographs, and cardiac enzyme, complete blood cell count, prothrombin time/INR, partial thromboplastin time, electrolyte, glucose, blood urea nitrogen, creatinine, and erythrocyte sedimentation rate tests. Final diagnoses at discharge also incorporated information from the subsequent clinical course and additional diagnostic tests, including VDRL, cholesterol panel, and transthoracic echocardiography for all patients and transesophageal echocardiography, transcranial Doppler, carotid duplex ultrasound, cerebral angiogram, cerebrospinal

Figure 3. Comparison chart of TOAST stroke subtype diagnoses based on history/examination with CT of head (if not, conventional MR with T1-, T2-weighted images) findings before MRA/DWI, after MRA alone, after DWI alone, after MRA+DWI, and final diagnosis after all the work-ups are completed.
RESULTS

A total of 46 patients (22 men and 24 women) who underwent DWI/MRA within 24 hours of admission of stroke onset were identified. Of these, 39 underwent CT scanning before MRI, whereas 7 proceeded directly to MRI. Thirty-eight patients presented with stroke to the emergency department (ED), whereas 8 patients developed stroke in the hospital.

Of the 38 patients presenting to the ED, 33 patients underwent CT scanning of the head. The average time from ED arrival to CT scan was a median of 1.25 hours and a mean of 2.00 hours (range 0.5 to 13 hours). The average time from ED arrival to MRI for the 38 patients was a median of 4.3 hours and a mean of 7.7 hours (range 1 to 23 hours). For the entire cohort, the average time from stroke onset to CT was a median of 10.0 hours and a mean of 21.9 hours (range 0.5 to 180 hours). The average time from stroke onset to MRI was a median of 19.0 hours and a mean of 32.3 hours (range 2 to 190.5 hours).

The acute ischemic lesion was visualized in 6 of 39 (15%) patients on CT, 33 of 45 (73%) patients on T2-weighted MRI, and 45 of 46 (98%) on DWI. Multiple acute lesions on DWI (suggesting embolism) were seen in 6 patients (13%). Among the 46 patients studied, intracranial MRA visualized stenoses or occlusions in vessels relevant to the areas of ischemia in 7 patients (15%), and extracranial MRA visualized relevant stenoses or occlusions in 3 patients (7%).

Data regarding the impact of DWI and MRA imaging on diagnostic accuracy with the use of TOAST methods are shown in Tables 1 and 2 and Figure 2. Figure 3 illustrates the impact of serial diagnostic testing in each of the patients in the cohort. Overall, the percent of cases matching final classification improved from 48% before DWI or MRA imaging to 56% with the addition of MRA alone, 83% with the addition of DWI alone, and 94% with the addition of combined DWI and MRA. In the large-vessel atherothrombembolic category, pre-MRI diagnoses matched final diagnoses in 56% of patients and improved to 89% with the addition of MRA alone, 56% with the addition

<table>
<thead>
<tr>
<th>Initial Oxfordshire Diagnosis (Before DWI)</th>
<th>Final Oxfordshire Diagnosis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Total Anterior</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Total anterior</td>
<td>3</td>
</tr>
<tr>
<td>Partial anterior</td>
<td>0</td>
</tr>
<tr>
<td>Lacunar</td>
<td>0</td>
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<tr>
<td>Posterior</td>
<td>0</td>
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<tr>
<td>Total</td>
<td>3</td>
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<table>
<thead>
<tr>
<th>Initial Oxfordshire Diagnosis (After DWI)</th>
<th>Final Oxfordshire Diagnosis</th>
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<tbody>
<tr>
<td></td>
<td>Total Anterior</td>
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<td>Total anterior</td>
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<td>0</td>
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<tr>
<td>Posterior</td>
<td>0</td>
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<tr>
<td>Total</td>
<td>3</td>
</tr>
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</table>
of DWI alone, and 89% with the addition of combined DWI and MRA. In the small-vessel lacunar category, pre-MRI diagnoses matched final diagnoses in 35% of patients, improving to 35% with the addition of MRA alone, 96% with the addition of DWI alone, and 100% with the addition of combined DWI and MRA. In the cardioembolic category, pre-MRI diagnoses matched final diagnoses in 40% of cases, changing to 40% with the addition of MRA alone, 80% with the addition of DWI, and 80% with the addition of combined DWI and MRA.

Data regarding the impact of imaging on Oxfordshire classification are shown in Tables 3 and 4. The overall percent of cases classified correctly improved from 67% before DWI to 100% after DWI.

Illustrative cases in which early MRI altered the diagnosis are shown in Figures 4 to 6.

**Figure 4.** The CT scan of a 63-year-old woman with acute-onset isolated right arm weakness performed 11.75 hours after the onset was normal. MRI was performed 13.5 hours after onset, which was 3 hours after admission. A, T2-weighted images were normal. Diffusion-weighted sequences showed lesions (arrows) of right frontal lobe white matter (B), left occipital pole and posterior right temporal lobe (C), and left motor strip (D), consistent with multiple emboli. ADC sequences showed correlation of low intensity at all sites, consistent with acute ischemia. TOAST diagnosis changed from stroke of undetermined etiology to cardioembolic. Transesophageal echocardiogram demonstrated marantic endocarditis.

**Figure 5.** The CT scan of a 67-year-old man with dysarthria and right facial droop on awakening performed 17.25 hours after onset showed no lesion. MRI was performed 36.5 hours after onset, which was 21.5 hours after admission. A, T2-weighted MRI showed multiple foci of increased signal in bilateral deep white matter (arrows). B, DWI demonstrates acute lesion in left posterior internal capsule. ADC sequences showed correlation of low intensity, consistent with acute ischemia. C, MRA displayed stenotic left M1 portion of middle cerebral artery (arrow) and atherosclerotic irregularity of cavernous portion of left internal carotid artery (arrow). TOAST diagnosis changed from small-vessel etiology to more than 1 likely etiology (both large-vessel atherothromboembolic and small-vessel possible).
Discussion

Early classification of ischemic stroke subtype is of substantial practical clinical value.\textsuperscript{28,29} Classification aids early prognostication, identifying patients at increased risk of early neurological worsening, early recurrent stroke, medical complications, need for discharge to a long-term care facility, and long-term death and disability.\textsuperscript{30,31} Long-term secondary prevention therapies differ significantly among ischemic stroke subtypes. For example, surgical endarterectomy is pursued for large-vessel carotid atherothrombotic disease, anticoagulation is pursued for atrial fibrillation and other causes of cardioembolism, and antiplatelet therapy is pursued for lacunar stroke. Earlier subtype diagnosis allows earlier planning for institution of the appropriate long-term therapy and earlier hospital discharge.

In addition, many clinicians tailor acute stroke treatment strategies to stroke subtype. Large-scale clinical trials have not yet demonstrated differential treatment effects among subtypes, but this in part may reflect imprecise entry stroke subtype diagnosis. Accurate early stroke subtype diagnosis will likely be critical for the conduct of clinical trials of emerging neurointerventional recanalization therapies.\textsuperscript{32} Trials of intra-arterial thrombolysis,\textsuperscript{33} acute cerebral angioplasty,\textsuperscript{34} and other endovascular reperfusion techniques require rapid, accurate identification of patients with large vessel occlusions.

Our data demonstrate that early, multimodal DWI/MRA substantially improves the accuracy of stroke subtype diagnosis. Marked improvements in matching final diagnosis were noted for both of the formal subtyping methods in widespread use: the TOAST and the Oxfordshire classification systems.

With the TOAST method, early DWI/MRA substantially improved the classification accuracy of early diagnoses of large-vessel atherothromboembolic and small-vessel (lacunar) subtypes. A tendency toward improved accuracy for diagnosis of cardioembolic stroke was also noted, but conclusions were limited by small patient numbers. Cardioembolic strokes were likely underrepresented in our cohort due to an inherent limitation of MRI-dependent diagnosis strategies. Acute MRI studies cannot be obtained in a subset of patients with cardiac sources of embolism, including patients with cardiac pacemakers and patients who are hemodynamically unstable due to acute myocardial infarction or cardiac dysrhythmia.

It is noteworthy that the accuracy of stroke subtype diagnoses rendered after large-vessel imaging by MRA was substantially further improved by the addition of DWI determination of ischemic insult topography. This observation suggests limitations to acute diagnostic strategies that rely only on standard CT plus vessel imaging with ultrasound (carotid duplex and transcranial), CT angiography, or MRA. DWI of infarct topography further assisted subtype diagnosis in several ways, including (1) in distinguishing when classic lacunar syndromes were indeed due to small, deep infarcts \(<1.5\,\text{cm}^2\) in diameter versus due to larger territorial infarcts; (2) in conversely determining when nonclassic lacunar clinical syndromes were due to small, deep infarcts rather than to larger insults; (3) in indicating multiple acute lesions in more than 1 vascular territory in patients with only 1 symptomatic lesion, which is consistent with cardioembolism; and (4) in determining the acute, symptomatic lesion from among several chronic deep and cortical lesions.

An important limitation of the present study is that the gold standard, final diagnoses were not reached completely independent of the diagnostic test being evaluated. For this reason, we have not expressed our detailed results in terms of sensitivity, specificity, positive predictive value, and negative predictive value; it would not be entirely statistically sound to do so. However, because it has been conventional to provide these measures in similar studies,\textsuperscript{1} for comparison purposes only we note what our data would have yielded for the 2 most common diagnostic categories. In the large-vessel atherothromboembolic category, sensitivity and positive predictive values of initial TOAST diagnosis would have been 56% and 83%, improving to 89% and 100% with the addition of MRA alone, 56% and 100% with the addition of DWI alone, and 89% and 100% with the addition of combined MRA and DWI. In the small-vessel category, sensitivity and positive predictive values of initial TOAST diagnoses would have
been 35% and 73%, improving to 35% and 80% with the addition of MRA alone, 96% and 92% with the addition of DWI alone, and 100% and 96% with the addition of combined MRA and DWI. It is important to note that our data likely underestimate the usefulness of DWI and MRA imaging in stroke subtype diagnosis. Our quantitative analyses capture only the impact of imaging with DWI and MRA on changes in stroke subtype diagnosis and not the impact in strengthening the likelihood of initially correct subtype assignments. For example, in the large-vessel atherothromboembolic category, DWI findings often increased the likelihood of a large-vessel mechanism by demonstrating infarct topography compatible with large-vessel disease. Such a finding helps to move a diagnosis from “possible large-vessel atherothromboembolic” to “probable large-vessel atherothromboembolic.” Similarly, MRA often strengthened the likelihood of small-vessel disease by excluding a large-vessel stenosis or occlusion, making the diagnosis of small-vessel lacunar even more probable.

Several groups have explored in an informal manner the aspects of the impact of early DWI and MRA imaging on the early diagnosis of large-vessel syndrome, lacunar syndromes, but none have previously examined their effect on changes in stroke subtype diagnosis and not the impact in strengthening the likelihood of initially correct subtype assignments. For example, in the large-vessel atherothromboembolic category, DWI findings often increased the likelihood of a large-vessel mechanism by demonstrating infarct topography compatible with large-vessel disease. Such a finding helps to move a diagnosis from “possible large-vessel atherothromboembolic” to “probable large-vessel atherothromboembolic.” Similarly, MRA often strengthened the likelihood of small-vessel disease by excluding a large-vessel stenosis or occlusion, making the diagnosis of small-vessel lacunar even more probable.

Early diagnosis of large-vessel syndrome or lacunar even more probable.

In conclusion, imaging with DWI and MRA within 24 hours of hospitalization substantially improves the accuracy of early ischemic stroke subtype diagnosis. When initial management decisions and clinical trial eligibility are influenced by stroke subtype, day 1 multimodal MRI methodology would be advantageous as a guide to therapy and to clinical trial enrollment. In addition, early multimodal MRI allows the rapid initiation of planning for long-term secondary stroke prevention therapy differentiated by stroke subtype.

Acknowledgments

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References


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