Advantages of Adding Diffusion-Weighted Magnetic Resonance Imaging to Conventional Magnetic Resonance Imaging for Evaluating Acute Stroke

Maarten G. Lansberg, MD; Alex M. Norbash, MD; Michael P. Marks, MD; David C. Tong, MD; Michael E. Moseley, PhD; Gregory W. Albers, MD

Background: Accurate localization of acute ischemic lesions in patients with an acute stroke may aid in understanding the etiology of their stroke and may improve the management of these patients.

Objective: To determine the yield of adding diffusion-weighted magnetic resonance imaging (DWI) to a conventional magnetic resonance imaging (MRI) protocol for acute stroke.

Design: A prospective cohort study.

Setting: A referral center.

Patients and Methods: Fifty-two patients with a clinical diagnosis of acute stroke who presented within 48 hours after symptom onset were included. An MRI scan was obtained within 48 hours after symptom onset. A neuroradiologist (A.M.N.) and a stroke neurologist (G.W.A.) independently identified suspected acute ischemic lesions on MRI sequences in the following order: (1) T2-weighted and proton density–weighted images, (2) fluid-attenuated inversion recovery images, and (3) diffusion-weighted images and apparent diffusion coefficient maps.

Main Outcome Measures: Diagnostic yield and interrater reliability for the identification of acute lesions, and confidence and conspicuity ratings of acute lesions for different MRI sequences.

Results: Conventional MRI correctly identified at least one acute lesion in 71% (34/48) to 80% (39/49) of patients who had an acute stroke; with the addition of DWI, this percentage increased to 94% (46/49) (P<.001). Conventional MRI showed only moderate sensitivity (50%-60%) and specificity (49%-69%) compared with a “criterion standard.” Based on the diffusion-weighted sequence, interrater reliability for identifying acute lesions was moderate for conventional MRI (k=0.5-0.6) and good for DWI (k=0.8). The observers’ confidence with which lesions were rated as acute and the lesion conspicuity was significantly (P<.01) higher for DWI than for conventional MRI.

Conclusion: During the first 48 hours after symptom onset, the addition of DWI to conventional MRI improves the accuracy of identifying acute ischemic brain lesions in patients who experienced a stroke.

Arch Neurol. 2000;57:1311-1316

Diffusion-weighted magnetic resonance imaging (DWI) was developed 3 decades ago,1 but it was only recently that the ability to detect early ischemic changes in brain tissue with DWI has been described.2 Subsequently, several groups have studied the use of DWI in animal stroke models3,4 and in patients who have had an acute stroke.5-12 These studies have consistently reported that DWI is superior to T2-weighted (T2W) magnetic resonance imaging (MRI) for detecting acute ischemic lesions.

However, most previous human studies have not enrolled consecutive patients and, therefore, do not reflect the use of DWI in a general population of unselected patients who have experienced an acute stroke. In some studies, the MRI scans were reviewed blinded to clinical information, which does not mirror the typical clinical setting. Moreover, only one retrospective study,11 to our knowledge, has compared DWI with fluid-attenuated inversion recovery (FLAIR) imaging and proton density–weighted (PDW) MRI, 2 techniques that may be more sensitive than T2W MRI for localizing acute ischemic lesions.

Previously, a retrospective review was conducted of DWI findings in patients with presumed stroke. In this study, the median time from symptom onset until the MRI scan was 48 hours.
PATIENTS AND METHODS

PATIENT ELIGIBILITY

Between October 1, 1997, and December 31, 1998, all patients who presented to the Stanford Stroke Center, Stanford, Calif, with a presumed diagnosis of acute stroke were screened by a stroke neurologist for eligibility to participate. Eligible patients were at least aged 18 years, had a score of 2 or higher on the National Institutes of Health Stroke Scale, and presented for examination within 48 hours of symptom onset. When the exact time of symptom onset was unknown, the last time that the patient was known to be symptom free was used as the time of stroke onset. Exclusion criteria included enrollment in an investigational neuroprotective agent trial, stroke treatment with thrombolytic therapy, and contraindications to MRI scanning. Informed consent was obtained from each patient or from an appropriate family member. The study was approved by the Stanford University Human Subjects Committee.

MRI VARIABLES AND DATA PROCESSING

Magnetic resonance imaging examinations were performed on a 1.5-T Signa Magnet (General Electric, Milwaukee, Wis). For each sequence, 16 slices were acquired (slice thickness, 5 mm; gap, 2.5 mm; and field of view, 24 cm). T2-weighted images (repetition time, 4000 ms; and echo time, 90 ms) and PDW images (repetition time, 4000 ms; and echo time, 15 ms) were obtained with a fast spin echo pulse sequence (matrix size, 256 x 256). Single-shot echo planar DWI scans (repetition time, 6000 ms; and echo time, 110 ms) were obtained at a low and a high b value (0 and 849 s/mm²) in X, Y, and Z planes, with and without an inversion pulse, and were processed to yield FLAIR images, isotropic DWI scans, and “trace” apparent diffusion coefficient (ADC) maps.

STUDY PROCEDURES

All eligible patients were examined by a stroke neurologist, and a National Institutes of Health Stroke Scale score was determined. Based on the neurologic examination and without knowledge of radiological findings, the neurologist classified each stroke into 1 of 3 categories: (1) anterior circulation, small subcortical; (2) anterior circulation, cortical or large subcortical; and (3) posterior circulation. The presumed hemisphere of the stroke (right vs left) was also determined. An MRI scan was obtained within 48 hours after symptom onset and was obtained again after 30 days. Scans were cancelled or delayed if scan time was not available or at the patients’ or their families’ request. A neuroradiologist (A.M.N.) and a stroke neurologist (G.W.A.) were provided with the clinical classification and independently identified suspected acute ischemic lesions on the baseline sequences. The readers’ confidence that an identified lesion was acute was rated on a 5-point scale, in which 1 indicates “possibly acute”; 3, “probably acute”; and 5, “definitely acute.” Lesion conspicuity was also rated on a 5-point scale, in which 1 indicates “very poor conspicuity”; 3, “moderate conspicuity”; and 5, “very good conspicuity.” Scans were reviewed in the following order: (1) T2W/PDW sequence, (2) FLAIR sequence, and (3) DWI/ADC sequence. Observers were blinded to subsequent sequences but not to previous sequences when assessing a scan. For example, when the FLAIR images were reviewed, the observer was blinded to the DWI/ADC sequence but not to the T2W/PDW sequence. After review of the baseline examination, the 30-day follow-up T2W image was assessed for the presence of lesions that were identified on the baseline sequences.

The criterion standard for the diagnosis of acute stroke was the opinion of the stroke neurologist responsible for the primary care of the patient and was based on all available clinical and radiological data, including the 30-day T2W scan. Clinical symptoms that persisted for at least 24 hours and could not be explained by any other disease process were required. The criterion standard for the identification of acute ischemic lesions was based on the DWI/ADC assessment of the 2 observers. A lesion was considered acute if both observers rated the lesion acute on the DWI/ADC sequence (hyperintense on the DWI scan and hypointense on the ADC map). If the observers disagreed on whether a lesion was acute on the DWI/ADC sequence, an adjudicator (a neuroradiologist [M.P.M.]) reviewed the case and the majority opinion was adopted. Using these standards, we determined for each MRI sequence the following: (1) how often at least one acute lesion was correctly identified in patients who had experienced an acute stroke; (2) the sensitivity, specificity, and interrater agreement for identifying acute lesions; and (3) the mean confidence and conspicuity ratings of acute lesions. The sensitivity and specificity were not calculated for the DWI/ADC sequence because the criterion standard was based on the DWI/ADC assessment.

STATISTICAL ANALYSES

Statistical analyses were performed using computer software (GB-Stat; Dynamic Microsystems Inc, Silver Spring, Md). The diagnostic yield for the identification of ischemic lesions in patients with an acute stroke using T2W/PDW, FLAIR, and DWI/ADC sequences was compared with the McNemar test. χ² Statistics were used to describe the interrater agreement for identifying acute lesions. The Kruskal-Wallis test was used to compare, among the different imaging sequences, the mean confidence and conspicuity ratings of lesions determined to be acute by the DWI/ADC criterion standard. For each sequence, acute lesions could be included twice, once, or not at all, depending on whether they were rated as acute by both observers, one observer, or neither observer. The Dunn procedure was used to compare specific groups under the Kruskal-Wallis test. Data are given as mean ± SD unless otherwise indicated.

RESULTS

During the enrollment period of this study, 62 patients met the inclusion criteria. Of these, 52 patients agreed to participate. The baseline MRI scan was performed at
a mean of 29±15 hours (median, 28.5 hours) after symptom onset. Five patients underwent scanning within 12 hours after symptom onset. In one patient, no T2W/PDW image was obtained at baseline. The mean age at baseline was 71±13 years, and the mean National Institutes of Health Stroke Scale score was 7.5±7.0. The follow-up MRI scan, obtained at a mean of 34±9 days after symptom onset, was available for 31 of the 49 patients who had experienced a stroke. Two patients died before the end of the study; 9 withdrew or did not return to the clinic for their 30-day appointment; and, for 7, the follow-up scan could not be retrieved.

Of the 52 patients, 49 were determined to have had an acute ischemic stroke by the neurologist responsible for the primary care of the patient. Among all 52 patients, 127 lesions were rated as acute by at least one observer on at least one MRI sequence. Of these 127 lesions, 88 were determined to be acute by the DWI/ADC criterion standard.

Of the 52 patients, 3 were determined not to have had an acute stroke. In one, symptoms were believed to be due to the unmasking of prior neurologic deficits in the setting of an infection and congestive heart failure. The second patient’s symptoms were due to a vestibulopathy confirmed by electronystagmography, and the third had a transient ischemic attack. In all 3, one or more lesions were incorrectly rated as acute by both observers on T2W/PDW and FLAIR scanning, while no lesions were rated as acute on DWI. In 3 (6%) of 49 patients who were clinically diagnosed as having an acute stroke, neither observer identified a suspected acute lesion on the DWI/ADC sequence. In all 3 patients, the clinical diagnosis was a posterior circulation infarct, likely located in the brainstem. In 2 of these patients, no suspected acute lesion was identified on the T2W/PDW or FLAIR sequence, and in 1, a suspected acute lesion was identified on the T2W/PDW and FLAIR sequences. This lesion, however, had a high ADC value and, therefore, was likely not acute.

Each observer correctly identified at least one acute lesion on the DWI/ADC sequence in 46 (94%) of 49 patients who experienced a stroke. This was significantly higher than the percentages for T2W/PDW (34 [71%] of 48 patients for each observer) and FLAIR (39 [80%] of 49 patients for observer 1 and 36 [73%] of 49 patients for observer 2) sequences (P<.001, χ² test) (Figure 1). There was no statistically significant difference between the percentages for the FLAIR and the T2W/PDW sequences (P=.48, χ² test). Among patients who had an acute lesion on the baseline DWI scan and had a follow-up scan, at least one acute lesion could be confirmed on the follow-up T2W MRI scan in 26 (90%) of 29 patients by observer 1 and in 23 (79%) of 29 patients by observer 2. For 1 of the 3 patients in whom no acute lesion could be confirmed by either observer on the follow-up T2W MRI scan, an acute lesion was recognized on the baseline DWI/ADC, T2W MRI, and FLAIR sequences. For the other 2 patients, an acute lesion was recognized only on the DWI/ADC. Figure 2 shows an example of one patient’s baseline MRI sequences and the follow-up T2W MRI sequence.

The Table summarizes the sensitivity, specificity, and interrater agreement for identifying acute ischemic lesions using different MRI sequences. The DWI assessment of 9 lesions differed between the 2 observers. Five were rated as acute, and 4 were rated not to be acute by the adjudicator. These were all small lesions in patients with a larger acute lesion that was identified by both observers.

Figure 3 illustrates the mean confidence and conspicuity ratings of lesions determined to be acute by the DWI/ADC, criterion standard for each MRI sequence. The confidence and the conspicuity ratings were statistically significantly better (P<.01) for the DWI/ADC sequence than for T2W/PDW and FLAIR sequences. There were no statistically significant differences between values for T2W/PDW and FLAIR sequences.

This study demonstrates some of the advantages of adding DWI to a conventional MRI protocol for the evaluation of stroke in consecutive patients who underwent scanning within 48 hours after symptom onset. With DWI, at least one acute lesion was identified in 46 (94%) of 49 patients with a final diagnosis of stroke, compared with a yield of approximately three fourths (71%-80%) when using conventional MRI (T2W/PDW or FLAIR sequences). The 3 patients with no signs of infarction on DWI or conventional MRI were clinically diagnosed as having posterior circulation infarcts that were localized to the brainstem. These results are consistent with a previous study that reported false-negative DWI scan results in some patients with a presumed brainstem infarction. On the follow-up T2W MRI scan, reviewed unblinded to the findings of the initial DWI scan, no acute lesion could be identified in a few patients, who had acute lesions on the baseline DWI/ADC. This suggests that a DWI scan obtained during the first days after stroke onset may be more sensitive than a late T2W MRI scan for the identification of acute ischemic lesions. The inferior
conspicuity of ischemic lesions on T2W MRI vs DWI and the fact that lesions shrink during the first month after a stroke may account for the lower yield of lesions on follow-up T2W MRI scans compared with initial DWI scans.

Compared with a DWI/ADC criterion standard, the sensitivity and specificity for identifying acute lesions using conventional MRI (T2W, PDW, or FLAIR sequences) are only moderate (sensitivity, 50%-60%; specificity, 49%-69%). All studies investigating the sensitivity and specificity of DWI in patients with an acute stroke are complicated by the lack of true criterion standards for the diagnosis of stroke and the identification of acute lesions. Our study, and some previous reports, used the clinical diagnosis, based on all available clinical and radiological data, as the criterion standard for the diagnosis of stroke.

In other previous studies, the criterion standard for the identification of acute lesions has been the follow-up T2W MRI scan. This method has some limitations. First, on T2W MRI scans, it is difficult to differentiate new from old lesions. Second, small acute lesions may shrink during the follow-up period and may not be identifiable on a follow-up T2W MRI scan at a later time. This could result in an underestimation of the total number of acute lesions. In an attempt to

---

**Figure 2.** Baseline and follow-up magnetic resonance imaging (MRI) scans obtained from a 65-year-old woman 7 hours after the acute onset of left arm discoordination. While T2-weighted (T2W), proton density–weighted (PDW), and fluid-attenuated inversion recovery (FLAIR) images show no acute lesion, diffusion-weighted MRI (DWI)/apparent diffusion coefficient (ADC) sequence demonstrates an acute lesion in the right parietal lobe (arrows). This lesion is also seen on the follow-up T2W examination (arrow).

<table>
<thead>
<tr>
<th>MRI Sequence</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Observer 1</th>
<th>Observer 2</th>
<th>Observer 1</th>
<th>Observer 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2W/PDW</td>
<td>57</td>
<td>50</td>
<td>49</td>
<td>69</td>
<td>0.5 (0.4-0.7)</td>
<td></td>
</tr>
<tr>
<td>FLAIR</td>
<td>58</td>
<td>60</td>
<td>59</td>
<td>66</td>
<td>0.6 (0.5-0.7)</td>
<td></td>
</tr>
<tr>
<td>DWI/ADC</td>
<td>. . . . . . .</td>
<td>. . . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>0.8 (0.7-0.9)</td>
<td></td>
</tr>
</tbody>
</table>

* T2W indicates T2-weighted; PDW, proton density–weighted; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted magnetic resonance imaging; ADC, apparent diffusion coefficient; MRI, magnetic resonance imaging; CI, confidence interval; and ellipses, data not applicable.

Sensitivity, Specificity, and Interrater Agreement for the Identification of Acute Lesions Using T2W/PDW, FLAIR, and DWI/ADC Scanning*

---

©2000 American Medical Association. All rights reserved.

Downloaded From: on 05/17/2018
avoid these limitations, we used the majority opinion of the initial DWI/ADC assessment as the criterion standard for the identification of acute ischemic lesions. This approach has the disadvantage that it could lead to an overestimation of the total number of acute lesions. A recent study\(^\text{14}\) showed that, in some instances, lesions identified on an early DWI scan can be reversible. However, these cases involved patients treated with recombinant tissue-type plasminogen activator who underwent MRI scanning within a few hours of symptom onset.

This study was designed to assess the potential value of adding DWI to a conventional MRI protocol with or without FLAIR. The scans were, therefore, evaluated in sequence: T2W/PDW first, FLAIR second, and DWI/ADC last. Alternatively, in a study designed to determine differences between various imaging techniques, scans should be read independently. We considered the design of our study to be clinically relevant because, in practice, it is likely that DWI will be added to conventional MRI sequences rather than replace them. Although it is possible that the yield for the identification of acute ischemic lesions with DWI would have been lower if MRI sequences were evaluated independently, the results of a prospective study\(^\text{11}\) in which imaging sequences were evaluated independently were similar to the results of our study (diagnostic yield of DWI, 98% vs 94%).

Our findings regarding the diagnostic yield of DWI are largely in agreement with the results of several other previously reported studies. Sorensen et al\(^\text{7}\) studied 11 consecutive patients imaged within 10 hours after symptom onset. In 9 of the 11 patients, acute DWI lesions were present despite normal findings on the initial computed tomographic scan, conventional MRI sequences, or both. Lovblad et al\(^\text{9}\) retrospectively analyzed 194 patients with an initial clinical diagnosis of stroke in whom a DWI scan was obtained within 24 hours after symptom onset. They included 23 patients with a transient ischemic attack and 20 patients with symptoms due to nonstroke etiologies and reported good sensitivity and specificity for DWI scans in the diagnosis of acute stroke, but they did not compare these findings with those of conventional MRI. Gonzalez et al\(^\text{12}\) compared DWI with T2W and PDW MRI in 14 patients who experienced a stroke and in 8 control patients, all of whom underwent scanning within 6 hours after symptom onset. They concluded that DWI is more accurate than T2W and PDW MRI for diagnosing stroke in the very early phase.

van Everdingen et al\(^\text{11}\) compared T2W, PDW, FLAIR, and DWI sequences in 38 patients who had experienced a stroke. Scans were interpreted by one neuroradiologist blinded to clinical findings. In this study, DWI proved superior to T2W and PDW imaging, but was only marginally better than FLAIR imaging, while in our study, DWI was also superior to FLAIR imaging. The study methods used by van Everdingen et al differed from ours. They used a follow-up MRI scan as the criterion standard for the identification of acute lesions and thus did not include those lesions that could be identified on the initial DWI scan but not on

![Figure 3. The confidence with which lesions were rated as acute and the conspicuity of the acute lesions are given for each magnetic resonance imaging (MRI) sequence (data for both observers are averaged). The scale for the confidence rating is as follows: 1, "possibly acute"; 3, "probably acute"; and 5, "definitely acute." The scale for the conspicuity rating is as follows: 1, "very poor conspicuity"; 3, "moderate conspicuity"; and 5, "very good conspicuity." The y-axis error bars indicate 95% confidence intervals of the mean. Observers were more confident identifying lesions as acute on the diffusion-weighted MRI (DWI)/apparent diffusion coefficient (ADC) sequence than on the T2-weighted (T2W)/proton density-weighted (PDW) or fluid-attenuated inversion recovery (FLAIR) sequences (P < .01), and lesions were more conspicuous on the diffusion-weighted sequence than on the T2W/PDW or FLAIR sequences (P < .01).](image-url)
for a proximal source of emboli may be warranted. Further studies are under way to prospectively investigate the potential clinical relevance of DWI in the evaluation of acute stroke.

This prospective study of consecutive patients who experienced a stroke and who underwent imaging within 48 hours after symptom onset demonstrates several advantages of the addition of DWI to a conventional MRI protocol. Using DWI, at least one acute lesion could be identified in a greater percentage of patients who had experienced a stroke, the interrater agreement for identifying acute lesions markedly increased, and the observers' confidence with which acute lesions were rated as acute and the lesion conspicuity improved. Conventional MRI showed only moderate sensitivity and specificity for identifying acute ischemic lesions compared with a DWI/ADC criterion standard.

Accepted for publication February 22, 2000.

This study was supported by Janssen Pharmaceuticals, Titusville, NJ; grant 5R01NS34866 from the National Institutes of Health, Bethesda, Md; a grant from the Dutch Heart Association (Dr Lansberg) and a grant from the Dutch Brain Association (Dr Lansberg), Den Haag, the Netherlands; a grant from the VSB fund, Utrecht, the Netherlands (Dr Lansberg); and a grant from Philips Medical Instruments, Eindhoven, the Netherlands (Dr Lansberg).

We thank the patients who gave their time to participate in this study; Michael O'Brien, MD, and Andrew Woolfenden, MD, for patient care; and Stephanie Kemp for the logistical organization of the study.

Corresponding author: Gregory W. Albers, MD, Stanford Stroke Center, 701 Welch Rd, Building B, Suite 325, Palo Alto, CA 94304-1705.

REFERENCES