Acute Perfusion and Diffusion Abnormalities Predict Early New MRI Lesions 1 Week After Minor Stroke and Transient Ischemic Attack

Negar Asdaghi, MD, MSc; Bilal Hameed, MD; Monica Saini, MD; Thomas Jeerakathil, MD, MSc; Derek Emery, MD, MSc; Kenneth Butcher, MD, PhD

Background and Purpose—Transient ischemic attack and minor stroke are associated with high ischemic recurrence in the first week. We prospectively studied the correlation between baseline diffusion/perfusion deficits and development of new ischemic lesions.

Methods—Patients with transient ischemic attack and those with minor stroke (n = 50) underwent MRI at admission. Acute perfusion-weighted imaging deficit (Tmax + 2-second delay) and diffusion-weighted imaging (DWI) lesion volumes were measured planimetrically. Follow-up scans were examined for new DWI/fluid-attenuated inversion recovery lesions at Days 7 and 30.

Results—Twenty-eight patients (56%) had acute DWI lesions. New DWI lesions developed in 9 of 50 patients (18%) at 1 week and 11 of 50 (cumulative 22%) at 4 weeks. Patients with new infarcts were more likely to have baseline DWI lesions (χ² = 8.264, P = 0.003). Baseline DWI lesion volume was significantly larger in those who developed new lesions at Day 7 (median, 13.2 mL; interquartile range, 12 versus median 0.1 mL; interquartile range, 2 mL; P < 0.001) and Day 30 (11.1 mL; interquartile range, 13 mL versus 0.1 mL; interquartile range, 13 mL; P < 0.001). Thirty-eight patients had baseline perfusion-weighted imaging. Patients with recurrent lesions were more likely to have baseline perfusion deficits (χ² = 19.5, P < 0.0001). All new lesions developed within the baseline hypoperfused regions. Baseline DWI lesion volume predicted new lesion development at day 7 (OR, 1.17 per mL; CI, 1.05 to 1.30; P = 0.005) and Day 30 (OR, 1.39 per mL; CI, 1.03 to 1.26; P = 0.009) by regression analysis.

Conclusions—Early recurrence of stroke is much more likely in patients with larger baseline DWI and perfusion-weighted imaging lesions. MRI lesion “recurrence” appears to be related to completion of the natural history of the original cerebrovascular syndrome rather than de novo events in most patients. (Stroke. 2011;42:2191-2195.)

Key Words: diffusion-weighted MRI ■ MRI ■ transient ischemic attack
also tested the hypothesis that baseline tissue hypoperfusion is related to the development of new ischemic lesions in these patients.

Methods

Patients
Between March 2008 and March 2010 we prospectively recruited patients presenting to our emergency department with minor stroke, defined as National Institutes of Health Stroke Scale (NIHSS) of ≤3 or TIA within 48 hours of symptom onset. TIA was defined according to World Health Organization criteria. Patients were enrolled after informed consent was obtained and were excluded if they had contraindications to MRI, evidence of renal failure as defined by creatinine >160 μmol/L, glomerular filtration rate <40, evidence of intracerebral hemorrhage on CT scan, or other nonischemic lesions. Additional inclusion criteria were age >18 years and functional independence, defined as a modified Rankin Scale score ≤2. This was an observational study only and secondary stroke prevention measures were implemented in accordance with current practice guidelines.

Imaging Protocol
All patients had serial MRI brain scans completed on the day of study enrollment and 7 and 30 days later. Patients were imaged using an 8-channel phased array radiofrequency head coil (MRI Devices, Waukesha, WI) on a 1.5-T whole-body Siemens Sonata MRI scanner (Siemens Medical Systems, Erlangen, Germany). DWI was acquired with single-shot spin-echo diffusion echoplanar imaging, 220-mm field of view, 20 5-mm axial slices with a 1.5-mm gap, b value of 1000 s/mm² along 3 orthogonal directions, repetition time/echo time 2600/86 msec, GRAPPA R=2, and matrix size of 128×128 zero-filled to 256×256. Other sequences included axial and sagittal T1, axial T2, axial fluid-attenuated inversion recovery (FLAIR), and 3-dimensional time-of flight MR angiography of the intracranial circulation. Perfusion-weighted images were acquired using a gadolinium (0.1 mmol/kg) injection delivered through a power injector at 5 mL/s through an 18-g needle in an antecubital vein followed by 20 mL saline flush at the same rate and echoplanar gradient-echo (T2*) images acquired every 1.3 seconds for 80 seconds (18 axial 5 mm+1.5-mm gap slices at each time point).

Image Analysis
MRI sequences (DWI/apparent diffusion coefficient, FLAIR, and T2) were reviewed for the presence of ischemic lesions at each time point. MR angiography scans were assessed using source images and maximum intensity projection reformats for the presence of intracranial stenosis/occlusion.

Postprocessing of raw perfusion images was performed by a single investigator (N.A.). Raw T2* files were imported into custom Matlab 7.4 (The Mathworks) software (PGUI Perfusion Analysis Software; CFIN Aarhus University Hospital, 2007). A whole brain mask was drawn to include all cerebral regions and vessels within the scan range. An arterial input function was manually selected from the middle cerebral artery contralateral to the visible DWI lesion and a block circulat deconvolution algorithm was used to calculate voxelwise maps of Tmax (time to peak of the impulse response). Planimetric DWI lesion and perfusion-weighted imaging deficit volume measurements were performed using the Analyze software package (Biomedical Imaging Resource, Rochester, NY). DWI hyperintense lesion borders were defined using a semiautomated threshold intensity technique. Hypoperfused brain tissue was defined as those voxels with Tmax delay of >2 seconds.

Clinical Assessment and Patient Outcomes
All patients had detailed neurological assessments, including NIHSS and ABCD² scores at the time of enrollment and at Day 7 and Day 30 after enrollment. All patients underwent an MRI and MR angiography study as soon as possible after enrollment and were scheduled for follow-up imaging at Day 7 and Day 30.

Table. Baseline Patient Characteristics According to the Presence and Absence of DWI Lesion

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DWI-Negative (N=22)</th>
<th>DWI-Positive (N=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>71.5±11</td>
<td>70±10</td>
<td>0.64</td>
</tr>
<tr>
<td>Male (%)</td>
<td>13/22 (59.1%)</td>
<td>20/28 (71.4%)</td>
<td>0.361</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>0 (1)</td>
<td>2 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABCD², median (IQR)</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Clinical TIA</td>
<td>12/22 (54.5%)</td>
<td>4/28 (14%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time from onset to first MRI,</td>
<td>23.7 (31.1) h</td>
<td>25.9 (19.4) h</td>
<td>0.853</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>7 (2) d</td>
<td>7 (2) d</td>
<td>0.992</td>
</tr>
<tr>
<td>MRI, median (IQR)</td>
<td>4/22 (18%)</td>
<td>8/28 (28%)</td>
<td>0.393</td>
</tr>
<tr>
<td>Significant intracranial stenosis or occlusion</td>
<td>1/4 (7.1%)</td>
<td>12/24 (50%)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; TIA, transient ischemic attack; PWI, perfusion-weighted imaging; SD, standard deviation.

Statistical Analysis
Statistical analysis was performed using Statistical Package for Social Sciences Version 17.0. Independent sample t tests were used to test differences between normally distributed parameters such as age and serum glucose at presentation. Differences between ordinal and nonnormally distributed data such as NIHSS scores and ABCD² scores were assessed using the Mann-Whitney U test. Differences in proportions were assessed using Fisher exact test. Multivariate logistic regression was used to determine the relationship between baseline diffusion and perfusion volumes and new lesion development at Days 7 and 30.

Results

Baseline Characteristics
A total of 56 patients were enrolled. Six patients who had a baseline MRI completed were excluded from this analysis due to an absence of Day 7 MRI data (lost to follow-up [n=5]; claustrophobia [n=1]). Therefore, the current analysis was performed on 50 patients. The median age of the remaining 50 patients was 69.5 (interquartile range [IQR], 61 to 80) years and 33 (66%) were male. The median NIHSS and ABCD² scores were 1 (IQR, 0 to 1) and 5 (IQR, 5 to 6), respectively. The median time from onset of symptoms to first MRI was 24.6 hours (IQR, 19.7 to 41.4). The median time between the first and second MRI was 7 days (IQR 6 to 8) and between the second and third MRI was 23 days (IQR, 21 to 26).

Acute MRI Findings
At baseline, 28 of 50 (56%) patients had a DWI lesion, of whom MRI revealed an intracranial occlusion or significant stenosis in 8 (16%). Another 4 patients had isolated vessel stenosis (n=3)/occlusion (n=1) without baseline DWI lesions. The remaining 18 patients (36%) did not have either a DWI lesion or any vessel abnormalities.

Baseline characteristics of patients with and without DWI lesions are shown in the Table. The median NIHSS score in DWI-positive patients (2; IQR, 2) was significantly higher
likely to have a recurrent DWI lesion at Day 7 (\(P<0.003\); Fisher exact test) and a new DWI/FLAIR lesion by Day 30 (\(P=0.014\), Fisher exact test). In a multivariate analysis comparing the baseline DWI-positive and -negative patients, baseline NIHSS score was the only patient characteristic identified to be a potentially confounding factor between the 2 groups (Table).

Acute DWI Deficits and Recurrent MRI Lesion Development

A total of 11 of 50 patients (22%) had a new ischemic lesion on DWI/FLAIR by Day 30, 9 of 11 (82%) of which were evident on DWI at Day 7. Of the 9 recurrent lesions in the first week, 6 were clinically asymptomatic, 1 was associated with new neurological symptoms, and 2 patients had symptoms suggestive of progression of baseline deficits (ie, worsening of hemiparesis and extension of sensory loss). Patients with a baseline DWI lesion were significantly more likely to have a recurrent DWI lesion at Day 7 (\(P=0.003\), Fisher exact test) and a new DWI/FLAIR lesion by Day 30 (\(P=0.014\), Fisher exact test). In a multivariate analysis comparing the baseline DWI-positive and -negative patients, baseline NIHSS score was the only patient characteristic identified to be a potentially confounding factor between the 2 groups (Table).

DWI lesion volume at baseline was significantly larger in those who developed a new lesion at Day 7 (median, 13.2 mL; IQR, 12 versus median, 0.1 mL; IQR, 2 mL; \(P<0.001\)) and by Day 30 (11.1 mL; IQR, 13 mL versus 0.1 mL; IQR, 13 mL; \(P<0.001\)) as compared with those who did not. Multivariate logistic regression analysis, adjusting for differences in the NIHSS, indicated that the development of new lesions at Day 7 was predicted by DWI lesion volume (OR, 1.17 per mL; 95% CI, 1.04 to 1.32; \(P=0.009\)). Similarly, new lesion development by Day 30, adjusting for the same confounder, was also predicted by DWI lesion volume (OR, 1.14 per mL; 95% CI, 1.02 to 1.26; \(P=0.016\)). Severity of neurological symptoms, as measured by NIHSS, was not an independent predictor of new ischemic lesion recurrence by Day 7 (OR, 1.4; 95% CI, 0.74 to 2.60; \(P=0.29\)) or Day 30 (OR, 1.35; 95% CI, 0.76 to 2.40; \(P=0.30\)).

Acute Perfusion-Weighted Imaging Deficits and Recurrent MRI Lesion Development

Patients with tissue hypoperfusion evident on baseline perfusion-weighted imaging were significantly more likely to have a concomitant DWI lesion (12 of 13 [92%]) than those without perfusion abnormalities (12 of 25 [48%]; \(P=0.012\)). There was not a significant difference between the time from symptom onset to MRI scan in those with perfusion abnormalities (mean, 22.9 hours; SD, 13.4 hours) relative to patients with normal perfusion studies at baseline (mean, 34.8; SD, 23.1 hours; \(P=0.95\)). Recurrence of DWI lesions at Day 7 was significantly more frequent in patients with baseline tissue hypoperfusion (8 of 13 [61%]) than those without perfusion abnormalities (0 of 25 [0%]; \(P<0.001\), Fisher exact test). Perfusion-weighted imaging lesion volumes were larger in patients with recurrent lesions at 7 days (median, 61.2 mL; IQR, 67 mL) as compared with those without recurrent lesions (median, 0 mL; IQR, 0 mL; \(P<0.001\); Figure). All new lesions at Day 7 occurred within the initial hypoperfused tissue regions.

New ischemic lesions on DWI/FLAIR at Day 30 were also more likely to develop in those with perfusion abnormalities (9 of 13 [70%]) than those with normal blood flow (1 of 25 [4%]; \(P<0.001\)). One patient without baseline perfusion deficits developed a new ischemic lesion on Day 30 follow-up imaging.

Acute Intracranial Vascular Occlusion/Stenosis and Recurrent MRI Lesion Development

The relationship between intracranial vascular occlusions/stenoses and recurrent ischemic lesions was assessed using MR angiography. Intracranial vascular lesions were present in 12 of 50 (24%) patients. Patients with vascular lesions were more likely to have early ischemic recurrence at Day 7 (6 of 12 [50%]) relative to those with normal intracranial vessels (3...
of 38 [7%; \( P=0.003 \)]. New DWI/FLAIR lesions at Day 30 were also more likely to occur in patients with baseline intracranial vessel abnormalities (7 of 12 [58%]) relative to those without (4 of 38 [0%]; \( P=0.002 \)).

Discussion
This study confirms that a significant number of patients with minor stroke and those with TIA develop new lesions with repeat imaging. We have shown for the first time that the majority of new MRI lesions found on repeat imaging at 30 days are actually present within 1 week of the index event. We have also demonstrated that in most patients, these new lesions develop in tissue that is acutely hypoperfused. Thus, lesion “recurrence” in fact most often appears to be completion of the pathophysiological process that began with symptom onset.

Acute Cerebrovascular Syndromes
In this study, we included both patients with clinical TIA and those with minor stroke. We favor a tissue-based definition of acute stroke.\(^2\)\(^1\)\(^2\) In our study, 25% of patients with TIA actually had evidence of tissue injury on DWI. With respect to risk stratification, it has previously been shown that patients with clinically defined TIA, similar to patients with stroke, are at high risk for development of recurrent stroke, myocardial infarction, and vascular death.\(^1\)\(^2\)\(^2\)\(^3\)\(^2\) Our results and those of others\(^1\)\(^2\)\(^4\) indicate that patients with evidence of tissue compromise and vascular occlusion are at highest risk for recurrent events. Thus, MRI may be 1 of the more useful tools for risk stratification in these patients, because those without DWI lesions appear to be at very low risk for future stroke.

Risk of Recurrent Stroke After TIA/Minor Stroke
Recent prospective studies indicate that the risk of stroke after TIA or minor stroke may be as high as 12% at 1 month and 17% at 3 months.\(^1\)\(^2\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\) Most studies indicate the risk of “recurrence” is highest very early after the index event with half of the recurrent events occurring within the first 48 hours.\(^2\)\(^2\)\(^2\)\(^15\) It is therefore possible that some of the cases of recurrent stroke in the first 48 hours may represent the natural evolution of the initial minor stroke and not a recurrent event per se, which is consistent with our own findings.

Clinical Significance of New MRI Lesions
Despite active lesion development on MRI, the majority of our patients did not develop new or worsening neurological symptoms, which is consistent with a prior serial MRI study in patients with TIA and those with minor stroke.\(^3\) There is evidence, however, that these should not be thought of merely as epiphenomena. Silent ischemic infarcts and cerebral white matter lesions have been associated with an increased risk of development of symptomatic strokes,\(^3\)\(^4\) progressive cognitive decline,\(^3\)\(^5\) and dementia severity.\(^3\)\(^6\)\(^7\) Our results indicate that the degree of tissue damage, as measured by the volume of acute infarct, is a strong predictor of recurrent lesions. Interestingly, silent ischemic infarcts have also been correlated with the presence of occult cerebral hypoperfusion and reduced cerebrovascular reserve.\(^3\)\(^8\)

Similar to our results, previous perfusion studies have demonstrated evidence of tissue hypoperfusion in up to 33% of clinically asymptomatic patients with TIA.\(^3\)\(^9\)\(^10\)\(^11\) These studies did not find a consistent correlation between baseline tissue hypoperfusion and clinical and radiographic outcomes. However, an association between the presence and the extent of perfusion abnormalities and recurrent ischemic lesions has not been previously reported. In our study, we found that patients with early radiographic recurrence are more likely to have hypoperfusion at baseline. Therefore, the apparent early “recurrence” of ischemia in these cases represents the natural evolution of the ischemic process and “completion” of infarct within the territory of the penumbral deficit.

Our study has a number of limitations, including a smaller and nonconsecutive sample size that may subject our findings to sampling bias. Furthermore, it may be argued that our patients do not represent a “true” TIA population, because those who developed new lesions in fact had evidence of tissue injury at baseline, that is, stroke. We would submit, however, that this is in fact the case in all TIA studies, and only acute DWI can differentiate transient ischemia without infarction from minor stroke. For this reason, we therefore believe it is appropriate to consider patients with TIA and those with minor stroke to represent a continuum determined by severity and duration of hypoperfusion.

Conclusions
MRI lesion “recurrence” appears to be related to completion of the natural history of the original cerebrovascular syndrome rather than de novo events in most patients with TIA/minor stroke. Our results suggest that patients with nondisabling stroke without evidence of baseline tissue injury or hypoperfusion are at lower risk for recurrent ischemic events. Diffusion and perfusion imaging characteristics can be used in conjunction with the patient’s clinical characteristics to identify high-risk patients.

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Disclosures
None.

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