CT-NIHSS Mismatch Does Not Correlate With MRI Diffusion-Perfusion Mismatch

Steven R. Messe MD; Scott E. Kasner MD; Julio A. Chalela MD; Brett Cucchiara MD; Andrew M. Demchuk MD; Michael D. Hill MD; Steven Warach MD

Background and Purpose—MRI diffusion-perfusion mismatch may identify patients for thrombolysis beyond 3 hours. However, MRI has limited availability in many hospitals. We investigated whether mismatch between the Alberta Stroke Program Early CT Score (ASPECTS) and the NIH Stroke Scale (NIHSS) correlates with MRI diffusion-perfusion mismatch.

Methods—We retrospectively analyzed a cohort of consecutive acute ischemic stroke patients who underwent MRI and CT at admission. NIHSS was performed by the admitting physician. MRI and CT were reviewed by 2 blinded expert raters. Degree of MRI mismatch was defined as present (>25%) or absent (<25%). Univariate and multivariate analyses were performed to determine characteristics associated with MRI mismatch. Probability of MRI mismatch was calculated for all combinations of ASPECTS and NIHSS cutoff scores.

Results—Included in the analysis were 143 patients. Median NIHSS on admission was 4 (IQR, 2 to 10); median ASPECTS was 10 (IQR, 9 to 10). Median time to completion of MRI and CT was 4.5 (2.5 to 13.9) hours after onset. CT and MRI were separated by a median of 35 (IQR, 29 to 44) minutes. MRI mismatch was present in 41% of patients. In multivariate analysis, only shorter time-to-scan (OR, 0.96 per hour; 95% CI, 0.92 to 1.0; P=0.043) was associated with MRI mismatch. There was no combination of NIHSS and ASPECTS thresholds that was significantly associated with MRI mismatch.

Conclusions—ASPECTS-NIHSS mismatch did not correlate with MRI diffusion-perfusion mismatch in this clinical cohort. MRI mismatch was associated with decreasing time from stroke onset to scan. (Stroke. 2007;38:2079-2084.)

Key Words: cerebral infarct | computed tomography | ischemic penumbra | magnetic resonance imaging | mismatch | neuroradiology | thrombolysis

A central premise of acute stroke treatment is the rapid restoration of blood flow to hypoperfused brain tissue that has not yet been irreversibly damaged. The only FDA-approved medical treatment at this time is tissue plasminogen activator (tPA), which is limited to a 3-hour time window. Unfortunately, the majority of stroke patients are not eligible for treatment because they present at the hospital too late. MRI diffusion-perfusion mismatch may be able to define a subset of patients with clinically meaningful ischemic penumbra beyond 3 hours, thereby extending the time window for safe and effective thrombolytic treatment. However, MRI has limited availability at many institutions, and there are inherent difficulties in acquiring rapid MRI scans in acute stroke patients. Thus, alternative strategies for identifying potentially salvageable brain tissue are desirable.

A mismatch between clinical deficit and CT findings has been suggested as a possible alternative approach. Specifically, a severe deficit in a patient with a normal or near-normal CT might be indicative of viable tissue. In this study we sought to determine whether a mismatch between the Alberta Stroke Program Early CT Score (ASPECTS) and the National Institutes of Health Stroke Scale (NIHSS) correlates with concurrent MRI diffusion-perfusion mismatch.

Materials and Methods

We retrospectively analyzed a cohort of consecutive ischemic stroke patients who presented to the National Institutes of Health Stroke program at Suburban Hospital in Bethesda, Maryland. All patients in the acute stroke clinical database, which included all patients who were admitted to the hospital with the diagnosis of an acute ischemic stroke, were eligible for this analysis. Multimodal MRI and noncontrast CT were attempted in all patients at admission as part of the routine imaging protocol. Patients were examined by the admitting stroke neurologist and the NIHSS was recorded. Stroke severity was determined using the NIHSS and categorized by approximate tertiles as 0 to 3, 4 to 9, or 10.

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From Department of Neurology (S.R.M., S.E.K., B.C.), University of Pennsylvania Medical Center, Philadelphia; Departments of Neurology and Neurosurgery (J.A.C.), Medical University of South Carolina, Charleston; Department of Clinical Neurosciences (A.M.D., M.D.H.), University of Calgary, Alberta, Canada; National Institutes of Health (S.W.), Bethesda, MD.

Correspondence to Steven R. Messé, MD, Department of Neurology, Comprehensive Stroke Center, University of Pennsylvania Medical Center, 3W Gates Building, 3400 Spruce Street, Philadelphia, PA 19104. E-mail: messe@mail.med.upenn.edu

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CT Data
CT scans were performed on a fourth-generation Somatom Plus (Siemens) or Lightspeed (General Electric) scanner. Images were acquired after the orbito-meatal plane with 5-mm thickness for the entire examination. Conventional brain window images were used. Each head CT was evaluated independently by 2 expert raters blinded to clinical information using the ASPECTS system. The ASPECTS scale divides the middle cerebral artery (MCA) territory into 10 divisions; 1 point is subtracted for each division that demonstrates ischemic changes. Vascular territories other than the MCA are not scored. A score of 10 indicates no early ischemic change and a lower score indicates greater changes. To increase the sensitivity of ASPECTS for identifying early ischemic change on head CT, disagreements in ASPECTS rating were resolved by averaging the 2 scores and rounding down. For the primary analysis, ASPECTS of 10 (ie, a completely normal MCA territory on CT scan) was compared with all other scores. Subsequent analyses assessed all other ASPECTS thresholds (9 and 10 versus lower scores, etc).

MRI Data
MRI was performed using a 1.5-T (Twinspeed XL; General Electric) system. The protocol consisted of diffusion-weighted imaging, fluid-attenuated inversion recovery, gradient recall echo, and perfusion-weighted imaging series, with a 24-cm field of view, 7-mm-thick axial-oblique slices aligned with the anterior–posterior commissure, and 20 contiguous slices interleaved, and colocalized. Diffusion-weighted images were acquired with repetition time/echo time=6.00/72 msec, an acquisition matrix of 128×128, and with both b=0 and b=1000 isotropically weighted, using fluid-attenuated inversion recovery T2-weighted imaging with a fast-spin echo sequence having TR/TE=9000/85msec, TI=1750 msec and a 256×128 matrix, and using gradient recall echo T2* imaging with TR/TE=800/20 msec and a 256×192 matrix. Perfusion-weighted images were obtained by injecting gadolinium (0.1 mmol/kg dose via power injector) with gradient-echo echo planar imaging, a TE of 45 msec; 25 phases with 2 seconds per phase, and a matrix of 64×64. Maps of normalized mean transit time (MTT) were calculated using concentration–time curves obtained from the perfusion-weighted imaging time series. The first moment of the concentration–time curve divided by the zero moment was directly normalized by a calculated reference, providing an estimate of a relative fractional change in MTT that does not depend on cerebral blood flow or volume. The reference was obtained by averaging the concentration–time data for all voxels in the brain. The resulting MTT images had nominal values of 1 for normal tissue, and >1 for ischemic tissue (where 1.5 corresponds to a 50% increase in MTT). Each MRI was evaluated by 2 expert raters blinded to clinical information for diffusion and perfusion defects, the latter defined by MTT. The vascular territory for each stroke was determined by each reviewer based on diffusion imaging analysis. Degree of mismatch was qualitatively determined based on simultaneous visual inspection of the 2 scans, a method that has been previously described and validated. Mismatch was defined as absent if the perfusion defect was <25% larger than diffusion abnormality. If MRI mismatch was present, the degree was noted as >25%, >50%, >75%, or 100%. Disagreement between the 2 MRI raters was resolved by consensus determination.

Statistical Analysis
Logistic regression was performed to determine which clinical characteristics were associated with MRI mismatch. Univariate analysis was performed to identify the relationships between MRI mismatch and the following variables: NIHSS, ASPECTS, and time to scan. Multivariate analysis was performed to determine the independent effect of each of these parameters on the likelihood of identifying MRI mismatch. From the multivariable models, the probability of mismatch could be estimated for each NIHSS and ASPECTS category with adjustment for time to scan. A Wald test was used to determine if each set of NIHSS and ASPECTS categories were associated with MRI mismatch after adjustment for time to scan. To confirm the findings of the Wald test, a likelihood ratio test was performed by comparing full models including NIHSS, ASPECTS, and time to scan with simpler models including only NIHSS and ASPECTS category with adjustment for time to scan. In the analysis compared with those without complete data were not significantly different and are displayed in Table 1. The distribution of ASPECTS and NIHSS scores at baseline are

TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Complete Data n=143</th>
<th>Incomplete Data* n=136</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (±SD), yr</td>
<td>71±17</td>
<td>73±17</td>
<td>0.22</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>68%</td>
<td>59%</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26%</td>
<td>19%</td>
<td>0.19</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>22%</td>
<td>15%</td>
<td>0.11</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>20%</td>
<td>19%</td>
<td>0.71</td>
</tr>
<tr>
<td>Smoking</td>
<td>16%</td>
<td>19%</td>
<td>0.60</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>27%</td>
<td>28%</td>
<td>0.77</td>
</tr>
<tr>
<td>Median time to complete scanning in hours (IQR)</td>
<td>4.5 (2.5–13.9)</td>
<td>4.3 (2.6–14.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Received IV IPA</td>
<td>18%</td>
<td>15%</td>
<td>0.33</td>
</tr>
<tr>
<td>Received IA IPA</td>
<td>2%</td>
<td>4%</td>
<td>0.42</td>
</tr>
<tr>
<td>Median NIHSS (IQR) on admission</td>
<td>4 (2–10)</td>
<td>5 (2–12)</td>
<td>0.34</td>
</tr>
<tr>
<td>Mean NIHSS (±SD) on admission</td>
<td>7.5±8.5</td>
<td>8.2±8.8</td>
<td>0.48</td>
</tr>
<tr>
<td>Median ASPECTS (IQR)</td>
<td>10 (9–10)</td>
<td>10 (9–10)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

*Subjects with incomplete data were missing CT, MRI, time of onset, or admission NIHSS.
depicted graphically in Figure 1. Among patients included in the analysis, the median NIHSS on admission was 4, IQR, 2 to 10). The median ASPECTS was 10 (IQR 9 to 10). The median time to completion of scanning was 4.5 (IQR 2.5 to 13.9) hours after onset. CT and MRI were separated by a median of 35 (IQR 29 to 44) minutes. The inter-rater reliability was good for ASPECTS score, with a quadratic-weighted kappa of 0.75 (95% CI, 0.59 to 0.90). Inter-rater reliability was excellent for determination of MRI mismatch, with a quadratic-weighted kappa of 0.95 (95% CI, 0.82 to 1.0). Overall, MRI mismatch was present in 58 of 143 (41%) patients. Based on diffusion MRI review, 104 of 143 (73%) of strokes in this cohort occurred within the MCA territory.

In univariate analysis, MRI mismatch was associated with higher NIHSS scores (referent group NIHSS 0 to 3: OR, 1.0 [referent]; NIHSS 4 to 10: OR, 2.2 [95% CI, 1.1 to 4.3; P=0.03]; NIHSS ≥10: OR, 2.2 [95% CI, 1.1 to 4.4; P=0.03]) and shorter time to scan (OR, 0.97 per hour [95% CI, 0.94 to 1.0; P=0.03]), but there was no association with ASPECTS 10 versus ≥10 (OR, 0.80 [95% CI, 0.42 to 1.53; P=0.51]) or with any other ASPECTS threshold. Figure 2 displays the decreasing predicted probability of MRI mismatch with longer time to scan.

In multivariate analysis, only shorter time to scan (OR, 0.96 per hour; 95% CI, 0.92 to 1.0; P=0.043) was associated with MRI mismatch. Neither NIHSS nor ASPECTS was associated with MRI mismatch after adjustment for time to scan. Consequently, there was no combination of NIHSS and ASPECTS thresholds that was significantly associated with MRI mismatch. Table 2 displays the time-adjusted predicted probabilities of MRI mismatch using NIHSS cutoffs for mild,
TABLE 2A. Predicted Probability of MRI Mismatch by NIHSS and ASPECTS Cutoffs, Adjusted for Time to Scan

<table>
<thead>
<tr>
<th>ASPECTS 10 (n=86)</th>
<th>ASPECTS 0–9 (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS 0–3 (n=68)</td>
<td>0.31 (0.20–0.44)</td>
</tr>
<tr>
<td>NIHSS 4–9 (n=36)</td>
<td>0.49 (0.30–0.67)</td>
</tr>
<tr>
<td>NIHSS ≥10 (n=39)</td>
<td>0.38 (0.22–0.58)</td>
</tr>
</tbody>
</table>

Wald test \( P=0.38 \) for entire sample, \( P=0.23 \) for those scanned within 6 hours. Likelihood ratio test \( P=0.95 \).

B. Predicted Probability of MRI Mismatch by NIHSS and ASPECTS Cutoffs, Adjusted for Time to Scan

<table>
<thead>
<tr>
<th>ASPECTS 9 or 10 (n=111)</th>
<th>ASPECTS 0–8 (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS 0–3 (n=68)</td>
<td>0.31 (0.21–0.44)</td>
</tr>
<tr>
<td>NIHSS 4–9 (n=36)</td>
<td>0.50 (0.33–0.67)</td>
</tr>
<tr>
<td>NIHSS ≥10 (n=39)</td>
<td>0.40 (0.23–0.59)</td>
</tr>
</tbody>
</table>

Wald test \( P=0.37 \) for entire sample, \( P=0.19 \) for those scanned within 6 hours. Likelihood ratio test \( P=0.79 \).

C. Predicted Probability of MRI Mismatch by NIHSS and ASPECTS Cutoffs, Adjusted for Time to Scan

<table>
<thead>
<tr>
<th>ASPECTS 8–10 (n=124)</th>
<th>ASPECTS 0–7 (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS 0–3 (n=68)</td>
<td>0.31 (0.21–0.44)</td>
</tr>
<tr>
<td>NIHSS 4–9 (n=36)</td>
<td>0.50 (0.34–0.67)</td>
</tr>
<tr>
<td>NIHSS ≥10 (n=39)</td>
<td>0.43 (0.25–0.62)</td>
</tr>
</tbody>
</table>

Wald test \( P=0.29 \) for entire sample, \( P=0.11 \) for those scanned within 6 hours. Likelihood ratio test \( P=0.41 \).

Discussion

Within this cohort of acute stroke patients seen in clinical practice, systematically interpreted head CT and clinical examination findings could not be validated as a means to identify ischemic penumbra as defined by MRI diffusion-perfusion mismatch. There have been a number of efforts to determine which patients may benefit from late thrombolysis. MRI has been used extensively to characterize the ischemic penumbra by identifying regions of brain with reduced blood flow, defined by perfusion-weighted imaging, and regions with irreversible neuronal injury, approximated by diffusion-weighted imaging. A mismatch between the volume of abnormality on diffusion and perfusion imaging appears to indicate viable penumbral tissue. MRI mismatch has been shown to correlate with favorable outcomes following late treatment with intravenous tPA up to 6 hours from symptom onset.\(^2,3,6,7\) The Desmoteplase in Acute Ischemic Stroke (DIAS) and Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trials demonstrated that thrombolysis may be effective up to 9 hours from the onset of symptoms in patients selected using MRI mismatch.\(^4,5\) Following-up on these promising preliminary data, there are currently at least 4 ongoing trials using MRI to select patients for thrombolysis beyond the 3-hour window, including Desmoteplase in Acute Ischemic Stroke-2 (DIAS-2), Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET), ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation (ROSIE), and MR and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE).

Unfortunately, while hyperacute MRI is a powerful tool, a large number of hospitals do not have the resources to obtain emergent MRI. A comprehensive survey of 180 hospitals in Illinois in 2002 found that only 73.9% had MRI availability, whereas only 25% and 17.2% were performing diffusion-weighted and perfusion-weighted imaging, respectively.\(^8\) Further, there are inherent difficulties in obtaining MRI from the emergency department in acute stroke patients. In 141 consecutive acute stroke patients, 19.9% were not able to undergo MRI.\(^9\) Half of these patients had MRI contraindications such as cardiac pacemakers, while the other half of patients were excluded from MRI because of decreased level of consciousness, vomiting, agitation, or hemodynamic compromise. A more practical alternative to determining the volume of ischemic penumbra would be tremendously valuable.

This study reports one of the largest series of acute stroke patients to undergo diffusion and perfusion MRI as part of a routine clinical practice. In multivariable analysis, we found that MRI mismatch correlated with time from symptom onset to scanning. Other studies of MRI mismatch have also found that time to scanning significantly impacts the presence of mismatch. A neurproptectant study of 81 acute stroke patients reported that 83% had MRI mismatch if scanned within 3 hours of symptom onset, whereas only 43% had mismatch at 24 hours.\(^14\) Overall, we found a relatively lower prevalence of MRI mismatch than has been reported in other series. This was most likely to be caused by the fact that we did not exclude patients based on stroke severity (milder strokes are presumably less likely to have a mismatch) or time to scanning (those who presented to the emergency room later, were less likely to have a mismatch). This relatively lower prevalence of MRI mismatch in our consecutive series of stroke patients is an important finding because it provides a more realistic assessment of how many patients may eventually be eligible for consideration of late thrombolysis if patient selection by MRI is determined to be beneficial.

We did not find any correlation between CT and NIHSS mismatch and MRI diffusion-perfusion mismatch. These results are generally consistent with other recent reports. In the NINDS rt-PA Stroke Study, baseline ASPECTS score had no effect on response to treatment with tPA given within 3
hours. A post-hoc analysis from the European-Australian Acute Stroke Study II (ECASS II) found that the benefit from tPA was not influenced by baseline ASPECTS. Similarly, a pooled analysis of patients enrolled in tPA clinical trials within 6 hours of symptom onset found that mismatch between ASPECTS and NIHSS did not reliably identify patients who were more or less likely to benefit from thrombolysis. A recent study of 825 patients with anterior circulation stroke treated with tPA did find a weak association with outcome. Our study is an important addition to the literature because we included patients who presented well beyond the 6-hour time window. Increased time from symptom onset is correlated with an increased likelihood of finding ischemic change on head CT. Thus, as time from symptom onset increases head CT becomes a more sensitive measure of irreversible ischemic injury, and thus is more analogous to diffusion MRI. The median time to presentation was 4.5 hours and 25% of patients presented after 14 hours, which should have improved the likelihood that CT findings would help to discriminate those patients with mismatch. Nevertheless, we did not find any utility of ASPECTS to determine MRI mismatch. The ECASS II data suggested that a lower ASPECTS was associated with a higher risk of thrombolysis-related hemorrhagic conversion. However, we did not study hemorrhage rates in our cohort as there were very few.

There are a number of limitations to this study that deserve mention. First, the median NIHSS was 4, and thus the majority of strokes in this series would be considered mild. As noted, milder strokes are probably less likely to have a large ischemic penumbra, and this is reflected in our relatively low rate of MRI mismatch. While the distribution of stroke severity in this cohort is consistent with what has been reported in other series of patients seen in clinical practice, a large cohort of exclusively severe strokes may be more likely to define an association. Second, the number of patients with incomplete data may have led to a biased result, although patient characteristics were similar whether the data were complete. Another important limitation is the fact that perfusion MRI remains an evolving and nonstandardized tool. The method we used to calculate MTT has been demonstrated to have the strongest association with clinical deficit in a cohort of patients imaged within 24 hours of stroke onset. Nevertheless, it is not clear whether MTT is the optimal measure of brain perfusion, particularly given the wide time window in our study. Finally, ASPECTS was originally designed to quantify ischemic change in MCA infarcts, whereas we included all stroke types in our analysis. In a retrospective analysis of the PROACT-2 study, which limited inclusion to patients with MCA occlusions, ASPECTS score was significantly associated with response to thrombolytic therapy. Based on diffusion MRI review, the majority of strokes occurred within the MCA territory in this cohort. This agrees with larger series of stroke patients seen in clinical practice. Limiting the analysis to those patients with stroke in the MCA territory did not reveal any significant associations. Further, it can be challenging to clinically distinguish between anterior and posterior circulation infarcts as well as between large-vessel and lacunar infarcts. Thus, we felt it was appropriate to include all stroke patients in our primary analysis.

In summary, mismatch between ischemic changes on head CT and clinical examination findings did not correlate with MRI diffusion-perfusion mismatch in this clinical cohort. MRI mismatch was associated with earlier time to scan. There are promising early data to suggest that MRI diffusion-perfusion mismatch will effectively extend the time window for thrombolysis in select patients and multiple ongoing studies are attempting to confirm this approach. Alternative methods to define the subset of acute stroke patients with clinically meaningful ischemic penumbra may also be demonstrated to be effective. A mismatch between clinical findings and diffusion MRI has been suggested as a means of avoiding the nonstandardized and not widely available perfusion MRI. Imaging protocols that provide information about the status of both the brain and the blood vessels such as multimodal CT, incorporating CT angiogram and CT perfusion, may also be demonstrated to be a practical approach.

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Disclosures
None.

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