Large Ischemic Lesions on Diffusion-Weighted Imaging Done Before Intravenous Tissue Plasminogen Activator Thrombolysis Predicts a Poor Outcome in Patients With Acute Stroke

Kazumi Kimura, MD; Yasuyuki Iguchi, MD; Kensaku Shibazaki, MD; Yuka Terasawa, MD; Takeshi Inoue, MD; Junichi Uemura, MD; Junya Aoki, MD

Background and Purpose—MRI is useful for detecting early ischemic lesions before administration of tissue plasminogen activator in patients with hyperacute ischemic stroke. However, it is unclear whether early ischemic change seen on diffusion-weighted imaging (DWI) can be used to predict patient outcomes.

Methods—Consecutive patients with anterior circulation ischemic stroke treated with tissue plasminogen activator within 3 hours of stroke onset were prospectively studied. The National Institutes of Health Stroke Scale score was obtained before and 7 days after tissue plasminogen activator administration. MRI, including DWI, was done before tissue plasminogen activator thrombolysis. The relationship between the DWI Alberta Stroke Programme Early CT Score (ASPECTS) and patients’ outcomes was assessed.

Results—The subjects consisted of 49 consecutive patients with stroke (27 males; mean age, 72.9 ± 10.3 years). The median (range) of the baseline DWI ASPECTS value was 9 (3–10). Dramatic improvement was seen in one of 8 patients with an ASPECTS  ≤ 5 compared with 21 of 41 patients with a DWI ASPECTS > 5 (P=0.0592). On the other hand, worsening was noted more frequently in patients with a DWI ASPECTS ≤ 5 (3 of 8 patients) than in patients with an ASPECTS > 5 (4 of 41 patients; P=0.0753). Bad outcome was seen more frequently in patients with a DWI ASPECTS ≥ 5 (6 of 8 patients) than in patients with a DWI ASPECTS > 5 (2 of 41 patients; P<0.0001). Multivariate logistic regression analysis demonstrated that a DWI ASPECTS ≤ 5 was the only independent predictor of a bad outcome (OR, 33.4; 95% CI, 2.7 to 410.8; P=0.0062).

Conclusion—DWI ASPECTS appears to be a reliable tool for predicting bad outcome. Patients with a DWI ASPECTS > 5 should be considered eligible for tissue plasminogen activator therapy. (Stroke. 2008;39:2388-2391.)

Key Words: outcome ■ tissue plasminogen activator ■ MRI ■ DWI ■ acute stroke

The intravenous administration of tissue plasminogen activator (tPA) can improve clinical outcome in patients with acute ischemic stroke.1,2 Diffusion-weighted MRI (DWI) findings are the earliest indicator of ischemic tissue changes. Therefore, an initial DWI should be a useful tool for diagnosing ischemic stroke. DWI growth has been correlated with clinical severity and final infarct size.3,4 However, it is unclear whether hyperacute ischemic change seen on DWI done before tPA infusion can predict patient outcomes.

If the DWI findings obtained before tPA thrombolysis can predict stroke outcome, then the DWI findings would offer important information before instituting tPA therapy. Barber et al introduced the Alberta Stroke Programme Early CT Score (ASPECTS) as a standardized quantitative CT grading system for patients with early stroke.5 ASPECTS is simple and quick and has good between-observer reliability. Therefore, we assessed the DWI findings in detection early signs of cerebral ischemia using ASPECTS.6 The aim of the present study was to elucidate whether DWI ASPECTS obtained before tPA thrombolysis could predict stroke outcome.

Subjects and Methods
Consecutive patients with acute ischemic stroke treated with tPA within 3 hours of stroke onset between October 2005 and November 2007 were studied. Only patients thought to have anterior circulation ischemia were included in the present study. Patients with heart valve replacements, pacemakers, or clipping of cranial arteries were excluded, because MRI is contraindicated in such patients. Inclusion and exclusion criteria for intravenous tPA were used in accordance with the Japan Alteplase Clinical Trial.7 A neurologist determined the National Institutes of Health Stroke Scale (NIHSS) scores before and 7 days after tPA infusion. The △NIHSS score was defined as the initial NIHSS score before tPA thrombolysis minus the NIHSS score 7 days after tPA infusion.

Received November 27, 2007; accepted December 13, 2007.
From the Department of Stroke Medicine, Kawasaki Medical School, Kurashiki City, Okayama, Japan.
Correspondence to Kazumi Kimura, MD, Department of Stroke Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama 701-0192, Japan. E-mail kimurak@med.kawasaki-m.ac.jp
© 2008 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.107.510917

2388
Three measures of clinical recovery based on modified methods used in previous studies were used. “Dramatic improvement” was defined as a \(/H_11350/10\)-point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. “Good improvement” was defined as a \(/H_11350/4\)-point reduction in the total NIHSS score. “Worsening” was defined as a \(/H_11350/4\)-point increase in the total NIHSS score. Symptomatic cerebral hemorrhage was defined as a \(/H_11350/4\)-point increase in the total NIHSS score. A bad outcome was defined as an NIHSS score \(/H_11350/20\) at 7 days after tPA infusion.

Before tPA infusion, MRI studies, including DWI, MR angiography, and T2*, were done to identify occluded arteries. Subsequently, follow-up T2* was performed 5 and 7 days after tPA administration to determine the presence or absence of intracerebral hemorrhage. The MRI was performed using a commercially available echoplanar instrument operating on a 1.5-T unit (Signa EXCITE XL version 11.0; GE Healthcare, Milwaukee, Wis). DWI ASPECTS was used to evaluate the affected middle cerebral artery territory. The presence of large artery occlusion was assessed using MR angiography. Occluded arteries on initial MR angiography were identified as follows: M1 occlusion, M2 occlusion, and internal cerebral artery occlusion.

Kappa statistics were used to assess the researchers’ agreement (KK, YI) on the DWI ASPECTS. Statistical analysis was performed using StatView version 5 statistical software. Spearman’s rank correlation coefficients were used to test the association between the baseline DWI ASPECTS value and the baseline NIHSS score and between the NIHSS score 7 days after tPA infusion and the \(\Delta\)NIHSS score. The significance of intergroup differences was assessed using Fisher exact test for categorical variables and the Mann–Whitney \(U\) test and the Kruskal-Wallis \(U\) test for continuous variables. Multivariate logistic regression analysis was performed to determine factors that could be considered to be independent predictors of worsening and bad outcome after tPA thrombolysis. Variables showing a value of \(P<0.1\) on univariate analysis were included in the multivariate model. Values of \(P<0.05\) were considered statistically significant.

All study protocols followed the principles outlined in the Declaration of Helsinki, and written informed consent was obtained from all patients.

Results

Sixty consecutive patients with stroke received tPA treatment. One patient was excluded because he had a pacemaker. Ten patients had a posterior circulation stroke. As a result, 49 patients (27 males, 22 females; mean age, 72.9 \(\pm\)10.3 years) were enrolled in the present study. The times from symptom onset to the initial MRI study and tPA bolus were 94.3 \(\pm\)30.3 minutes and 141.6 \(\pm\)27.1 minutes, respectively.

The median (range) of baseline NIHSS score was 14 (1–25). The median (range) of the baseline DWI ASPECTS value was 9 (3–10). The baseline DWI ASPECTS was correlated with the baseline NIHSS score \((r=-0.575, P<0.0001); Figure A\) and the 7-day NIHSS score \((r=-0.489, P=0.0004); Figure B\). Figure C shows the baseline DWI ASPECTS value and \(\Delta\)NIHSS. The correlation

![Figure A](http://stroke.ahajournals.org/)

![Figure B](http://stroke.ahajournals.org/)

![Figure C](http://stroke.ahajournals.org/)
Table 1. Univariate Statistics Between Patients With DWI ASPECTS ≤5 and >5

<table>
<thead>
<tr>
<th></th>
<th>DWI ASPECTS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤5 (N=8)</td>
<td>&gt;5  (N=41)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>75.8±8.2</td>
<td>72.3±10.6</td>
<td>0.2503</td>
</tr>
<tr>
<td>Female</td>
<td>5 (62.5%)</td>
<td>17 (41.5%)</td>
<td>0.4397</td>
</tr>
<tr>
<td>Time from symptom onset to treatment, minutes</td>
<td>145.0±27.9</td>
<td>141.0±27.2</td>
<td>0.6456</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (25.0%)</td>
<td>25 (61.0%)</td>
<td>0.1172</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (12.5%)</td>
<td>5 (12.2%)</td>
<td>0.9999</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1 (12.5%)</td>
<td>7 (17.1%)</td>
<td>0.9999</td>
</tr>
<tr>
<td>Right to left shunt</td>
<td>2 (25.0%)</td>
<td>15 (36.6%)</td>
<td>0.6964</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>0</td>
<td>4 (9.8%)</td>
<td>0.9999</td>
</tr>
</tbody>
</table>

with a DWI ASPECTS ≤5, the NIHSS score at 7 days was higher in the 8 patients than in 41 patients with a DWI ASPECTS >5 (21 of 41; P=0.0592; Table 1). On the other hand, worsening was more common in patients with a DWI ASPECTS ≤5 (3 of 8 patients) than in patients with a DWI ASPECTS >5 (4 of 41; P=0.0753; Table 2). Bad outcome was more common in patients with an ASPECTS ≤5 (6 of 8 patients) than in patients with a DWI ASPECTS >5 (2 of 41 patients; P<0.0001; Table 2). Symptomatic cerebral hemorrhage within 7 days after tPA infusion was observed in one patient with a baseline NIHSS score of 7 and a DWI ASPECT value of 11. T2* imaging showed an asymptomatic cerebral hemorrhage in 20 patients.

On multivariate logistic regression analysis using presence or absence of internal cerebral artery occlusion, baseline NIHSS score (≤15 versus >15), and DWI ASPECTS (≤5 versus >5) as variables showing P<0.1 on univariate analysis, DWI ASPECTS ≤5 was not an independent factor associated with worsening (OR, 7.5; 95% CI, 0.6 to 97.2; P=0.1212), but was independently associated with bad outcome (OR, 33.4; 95% CI, 2.7 to 410.8; P=0.0062).

Discussion

The present study demonstrated that the DWI ASPECTS was reliable and could predict a bad outcome.

In patients with a DWI ASPECTS value of 6 to 10 (n=41), combined dramatic and good improvement was seen in 68.3% and a bad outcome was seen in 4.9%. Clinical recovery after tPA infusion appears to depend on early recanalization of occluded arteries. Therefore, among patients with a DWI ASPECTS of 6 to 10, those with neurological improvement might have had early recanalization. However, among patients with a DWI ASPECTS ≤5, combined dramatic and good improvement was seen in only 25.0%, whereas 75.0% had a bad outcome. Therefore, even if

Table 2. Clinical Recovery, NIHSS Score, and Cerebral Hemorrhage on T2* 7 Days After tPA Treatment and Baseline DWI ASPECTS (≤5 versus >5) and NIHSS Score (≤15 Versus >15)

<table>
<thead>
<tr>
<th></th>
<th>Clinical Recovery</th>
<th>NIHSS Score at 7 Day</th>
<th>Cerebral Hemorrhage*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dramatic</td>
<td>Good</td>
<td>Worsening</td>
</tr>
<tr>
<td>DWI ASPECTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 (n=8)</td>
<td>1 (12.5%)</td>
<td>1 (12.5%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>&gt;5 (n=41)</td>
<td>21 (51.2%)</td>
<td>7 (17.0%)</td>
<td>4 (9.8%)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤15 (n=28)</td>
<td>14 (50.0%)</td>
<td>5 (17.9%)</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>&gt;15 (n=21)</td>
<td>8 (38.1%)</td>
<td>3 (14.2%)</td>
<td>5 (23.8%)</td>
</tr>
</tbody>
</table>

*Symptomatic (n=1) and asymptomatic (n=20) DWI ASPECTS: P=0.086 in the clinical recovery; P=0.0001 in the NIHSS score at 7 days; P=0.0263 in the cerebral hemorrhage. NIHSS score: P=0.086 in the clinical recovery; P=0.015 in the NIHSS score at 7 days; P=0.040 in the cerebral hemorrhage.
early recanalization after tPA infusion occurred in such patients, the ischemic damage was so severe that clinical recovery was not likely. Therefore, patients with a DWI ASPECTS >5 should be considered eligible for tPA therapy.

Barber et al reported that ASPECTS values of 7 or less of CT findings could predict poor functional outcome. Our results also show that a DWI ASPECTS ≤5 was independently associated with bad outcome after tPA thrombolysis. Our cutoff DWI ASPECTS value of 5 was lower than the value of 7 used by Barber et al, because DWI may be more sensitive than CT for detecting early ischemic changes.

The present study had several limitations. Perfusion-weighted MRI can detect hypoperfused tissue, and the combination of DWI and perfusion-weighted MRI may identify a penumbra area with normal DWI but with perfusion-weighted MRI showing hypoperfused tissue. However, to not delay the start of tPA treatment, we did not include perfusion-weighted MRI examinations in the present study. Second, it is more likely that there is a linear relationship between the amount of early ischemic changes and the functional outcome. We would need more patients to elucidate the issue.

In conclusion, the present study demonstrated that DWI ASPECTS was reliable and could predict a poor outcome. Poorer response to intravenous tPA therapy should be expected in patients with baseline DWI ASPECTS ≤5 and these patients should also be excluded from studies of thrombolysis beyond the 3-hour time window.

Sources of Funding
This study was supported in part by research grants for Cardiovascular Disease (18C-2) from the Ministry of Health, Labor and Welfare of Japan.

Disclosures
None.

References
Large Ischemic Lesions on Diffusion-Weighted Imaging Done Before Intravenous Tissue Plasminogen Activator Thrombolysis Predicts a Poor Outcome in Patients With Acute Stroke
Kazumi Kimura, Yasuyuki Iguchi, Kensaku Shibazaki, Yuka Terasawa, Takeshi Inoue, Junichi Uemura and Junya Aoki

Stroke. 2008;39:2388-2391; originally published online June 5, 2008; doi: 10.1161/STROKEAHA.107.510917
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/8/2388

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/