Transient Ischemic Attack and Stroke Can Be Differentiated by Analyzing Early Diffusion-Weighted Imaging Signal Intensity Changes

Kerstin Winbeck, MD; Kathrin Bruckmaier; Thorleif Etgen, MD; Helga Gräfin von Einsiedel, MD; M. Röttinger, MD; Dirk Sander, MD

Background—Diffusion-weighted imaging (DWI) has been established to diagnose acute cerebral ischemia. Signal intensity changes occur not only in patients with definite stroke but also in up to 67% of transient ischemic attack (TIA) patients. We investigated the predictive value of DWI signal intensity changes to distinguish between TIA and stroke.

Methods—Clinical data, conventional magnetic resonance imaging (MRI), and DWI were collected in 60 consecutive patients with TIA and 37 consecutive patients with stroke. DWI was performed within 24 hours after symptom onset. Using an image analyzing system, we calculated the ratio of the lesion and corresponding contralateral normal tissue average signal intensity (rAI).

Results—Eighteen of 60 TIA patients (30%) revealed focal abnormalities on DWI. The mean duration of symptoms was 5.3 hours in TIA patients with DWI lesions and 5.2 hours in patients without lesions. The time to DWI was comparable in TIA and stroke patients. Even within 6 hours after symptom onset, the signal intensity was significantly higher (P=0.03) in stroke patients (n=13, rAI=1.26) as compared with TIA patients with DWI lesions (n=9, rAI=1.16).

Conclusions—Our data indicate that already within 6 hours after symptom onset, TIA and stroke might be differentiated by analyzing the signal intensity of the lesions. (Stroke. 2004;35:1095-1099.)

Key Words: cerebral ischemia, transient stroke

Diffusion-weighted imaging (DWI) has become an established magnetic resonance imaging (MRI) technique for the diagnosis of acute cerebral ischemia. In most cases, this technique is superior to conventional MRI and computed tomography (CT). Interestingly, recent studies using DWI described relevant focal abnormalities in up to 67% of patients with clinical TIA. As a consequence of these findings, the transient ischemic attack (TIA) working group suggested a new definition of TIA as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms lasting <1 hour and without evidence of acute infarction. Kidwell et al performed DWI in TIA and stroke patients and reported a significantly less abnormal apparent diffusion coefficient (ADC) map in TIA as compared with stroke patients. However, none of the recent investigators analyzed the ability of DWI signal intensity changes to differentiate between TIA and stroke at early stages after symptom onset. We evaluated whether it is possible to differentiate TIA and minor stroke (NIHSS ≤5) by analyzing DWI signal intensities within a few hours after symptom onset. Regarding the recently proposed new definition of TIA, we evaluated the subgroup of TIA patients with a symptom duration of <1 hour and those with >1 hour in more detail.

Subjects and Methods

Selection of Patients

Between May 2000 and 2003, 762 first-ever ischemic stroke patients and 224 first-ever TIA patients have been treated at the stroke unit of the department of neurology. In 471 stroke patients, the DWI was performed during 24 hours after symptom onset; 434 stroke patients were excluded because of NIHSS score >5 (n=368) or brain stem or cerebellar infarction (n=66). The remaining 37 patients (NIHSS =5, 18 men, mean age 64.7 years; 95% confidence interval [CI]: 60.6, 68.9) were included. In the TIA group with anterior circulation symptoms (n=124), the DWI was performed within 24 hours after symptom onset in 60 patients (41 men, mean age 61.6 years). TIA was defined as an acute transient focal neurological deficit caused by vascular disease that reversed totally within 24 hours. The following data were collected: age, sex, duration of symptoms, time to DWI, body mass index, and presence of vascular risk factors as coronary artery disease, hypertension, diabetes mellitus, hypercholesterolemia, and atrial fibrillation. The clinical characteristics of the patients are given in Table 1.

MRI

MRI was performed within 24 hours after symptom onset in all patients. We performed transverse T1 (TR/TE 654/14 ms), transverse T2 (TR/TE 3305/132 ms), and at least 1 DWI sequence, usually a transverse and, in doubtful cases, a sagittal or coronal plane using a 1.5-Tesla MRI (Magnetom Symphony; Siemens Medical Systems). The DWI imaging parameters were: TR, 4006 ms; TE, 83 ms; slice thickness, 4 to 6 mm; gap, 1.5 mm; 128×128-pixel matrix; field of view...
average signal intensity (rAI) on b\textsubscript{1000}/H11005 images (rAI\textsubscript{b\textsubscript{1000}}) was 1.21, and it was 1.25 for the stroke patient. Generally, a value of 0.8 indicates good accuracy.\textsuperscript{14} If multiple lesions or noncontiguous abnormalities were noted, the ratio was calculated by summing up individual average intensities of all abnormal lesions and dividing the resulting value by the average intensity of the mirrored contralateral corresponding normal brain areas. Figure 1 gives an example for the measurement.

**Statistical Analysis**

All values are given as mean and 95% CI. Between-group comparisons were performed with χ\textsuperscript{2} and Student \textit{t} test for normally distributed data. For abnormally distributed data, the Wilcoxon test was used. A 1-way ANOVA was applied to analyze the signal intensity changes over time in TIA and stroke patients. Linear regression analysis was performed to evaluate the correlation between time to DWI and average signal intensity in TIA and stroke, as well as the symptom duration and the average signal intensity in TIA patients. \textit{P}<0.05 was considered significant.

Receiver operating characteristic (ROC) curves were constructed, plotting sensitivity versus 100% minus percent specificity to examine the predictive value for different rAI using Graph Pad Prism 4. Optimum cutoff values with the best combination of sensitivity and specificity were calculated. Overall accuracy of the diagnosis was expressed by the area under the curve, ranging from 0.5 to 1. A value of 1 implies perfect sensitivity and specificity, whereas a value of 0.5 implies that the model’s accuracy is not better than chance.\textsuperscript{13} Generally, a value of >0.7 can be interpreted as reasonable and a value >0.8 indicates good accuracy.\textsuperscript{14}

**Results**

**TIA Group**

Eighteen TIA patients (30%) showed focal abnormalities on DWI. The mean time to DWI did not differ significantly between the TIA patients with and without DWI signal intensity changes (Table 2). The basic characteristics of the TIA patients with and without DWI abnormalities are given in Table 2. The occurrence of DWI hyperintensity was not significantly associated with the duration of the TIA. The

![Figure 1. DWI and rAI measurement in a patient with TIA (left) and stroke (right) using the b=1000 image performed 8 hours after symptom onset in both cases. In the TIA patient, the rAI\textsubscript{b=1000} was 1.21, and it was 1.25 for the stroke patient.](Image 548 to 741)
mean duration of symptoms in TIA patients with pathological DWI was 5.3 hours and was 5.2 hours in patients without signal intensity changes. We found no correlation between the $rAI_{b\rightarrow 1000}$ and $rAI_{ADC}$ and TIA duration.

**TIA With Symptom Duration of 1 Hour or Less**
In 25 TIA patients, the symptoms disappeared within 1 hour. Eight of 25 (32%) of these patients showed signal intensity changes on DWI. This proportion of DWI changes was similar to the DWI abnormalities in TIA patients with symptom duration of >1 hour (29%) (Table 3). No significant differences for several cardiovascular risk factors, the time to DWI, the $rAI_{b\rightarrow 1000}$ and $rAI_{ADC}$ was found (Table 3).

**TIA With DWI During Symptoms**
In 19 TIA patients, the DWI was performed during symptom duration. The mean duration of symptoms was 10.4 hours (95% CI: 6.2, 14.6) and the mean time to DWI was 7.3 (95% CI: 3.6, 11.0). In 8 of 19 (42%) of these patients, the DWI showed signal intensity changes. The mean duration of symptoms and time to DWI was comparable in TIA with and without DWI lesions in this group. Moreover, the mean $rAI_{b\rightarrow 1000}$ and $rAI_{ADC}$ in TIA patients with (n=9) and without (n=9) symptoms during DWI were comparable ($rAI_{b\rightarrow 1000}$ 1.17 [95% CI: 1.09, 1.25] versus 1.17 [95% CI: 1.11, 1.22] and $rAI_{ADC}$ 0.86 [95% CI: 0.80, 0.91] versus 0.87 [95% CI: 0.79, 0.94]).

**Comparison of TIA and Stroke Patients**
We observed a significantly lower NIHSS in the TIA group and a higher incidence of atrial fibrillation in the stroke group. The other basic characteristics (vascular risk factors, the time to DWI, and the area of hyperintensity) were comparable (Table 1). There was no correlation between the

### TABLE 2. Demographic Data of the TIA Patients With and Without DWI Abnormality

<table>
<thead>
<tr>
<th></th>
<th>TIA With Hyperintensity</th>
<th>TIA Without Hyperintensity</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of patients</td>
<td>18</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.8 [55.5, 68.3]</td>
<td>61.5 [56.2, 66.8]</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>11/7</td>
<td>30/12</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of symptoms (h)</td>
<td>5.3 [1.8, 8.7]</td>
<td>5.2 [2.9, 7.5]</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.6 [25.0, 29.8]</td>
<td>26.7 [25.4, 28.0]</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (N)</td>
<td>13 (72%)</td>
<td>31 (74%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic heart disease (N)</td>
<td>3 (17%)</td>
<td>7 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia (N)</td>
<td>8 (44%)</td>
<td>13 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (N)</td>
<td>9 (50%)</td>
<td>17 (40%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (N)</td>
<td>4 (22%)</td>
<td>7 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation (N)</td>
<td>2 (11%)</td>
<td>1 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to DWI (h)</td>
<td>9.3 [5.2, 13.4]</td>
<td>13.2 [10.6, 15.9]</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values in square brackets indicate 95% confidence intervals.

NS indicates not significant.

### TABLE 3. Demographic Data of the TIA Patients With Duration of Symptoms Less Than 1 Hour and More Than 1 Hour

<table>
<thead>
<tr>
<th></th>
<th>TIA &lt;1 Hour</th>
<th>TIA =1 Hour</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of patients</td>
<td>25</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Abnormal DWI (N)</td>
<td>8 (32%)</td>
<td>10 (29%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (y)</td>
<td>59.6 [53.3, 66.0]</td>
<td>63.0 [57.6, 68.4]</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>17/8</td>
<td>24/11</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.6 [25.0, 28.2]</td>
<td>27.1 [25.5, 28.7]</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (N)</td>
<td>19 (76%)</td>
<td>25 (71%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic heart disease (N)</td>
<td>3 (12%)</td>
<td>7 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia (N)</td>
<td>8 (32%)</td>
<td>13 (37%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (N)</td>
<td>10 (40%)</td>
<td>16 (46%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (N)</td>
<td>2 (8%)</td>
<td>9 (26%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Atrial fibrillation (N)</td>
<td>1 (4%)</td>
<td>2 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to DWI (h)</td>
<td>12.6 [9.0, 16.1]</td>
<td>11.7 [8.7, 14.7]</td>
<td>NS</td>
</tr>
<tr>
<td>$rAI_{b\rightarrow 1000}$</td>
<td>1.17 [1.13, 1.21]</td>
<td>1.17 [1.13, 1.20]</td>
<td>NS</td>
</tr>
<tr>
<td>$rAI_{ADC}$</td>
<td>0.86 [0.78, 0.95]</td>
<td>0.86 [0.81, 0.91]</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values in square brackets indicate 95% confidence intervals.

NS indicates not significant.
and the time to DWI. Compared with TIA patients, in stroke patients, the \( r_{AI_{b=1000}} \) was significantly higher (1.30 versus 1.17, \( P < 0.001 \)) and the \( r_{AI_{ADC}} \) was significantly lower (0.73 versus 0.86; \( P < 0.001 \), Table 1).

The DWI was performed in 21 (35%) TIA and 14 (38%) stroke patients within 6 hours after symptom onset, in 12 (20%) TIA and 10 (27%) stroke patients between 6 and 12 hours after symptom onset, and in 27 (45%) TIA and 13 (35%) stroke patients between 12 and 24 hours after symptom onset. Eight TIA patients in the first group (38%), 4 in the second group (33%), and 6 in the third group (22%) showed DWI abnormalities. At all time intervals, the \( r_{AI_{b=1000}} \) (Figure 2 upper) and the \( r_{AI_{ADC}} \) (Figure 2, lower) were significantly different in stroke patients compared with TIA patients. Regarding the subgroup of TIA patients in whom the DWI was performed during symptoms, we also found a significant difference between the \( r_{AI_{b=1000}} \) (1.17 [95% CI: 1.13, 1.21]) versus 1.29 [95% CI: 1.26, 1.34]; \( P < 0.001 \)) and the \( r_{AI_{ADC}} \) (0.86 [95% CI: 0.80, 0.91] versus 0.73 [95% CI: 0.69, 0.77]; \( P = 0.01 \)) as compared with stroke patients.

ROC curve analysis revealed a good value for the area under the curve (0.85 for \( r_{AI_{b=1000}} \) and 0.82 for \( r_{AI_{ADC}} \); Figure 3). For \( r_{AI_{b=1000}} <1.21 \), the sensitivity for TIA was 78%, with a specificity of 76% and a positive predictive value of 89%. Concerning a \( r_{AI_{ADC}} >0.82 \), the sensitivity was 71%, the specificity 72%, and the positive predictive value 73%. For the combination of the ADC and \( b=1000 \) values, no improvement in sensitivity and specificity could be found using ROC curve analysis. We additionally performed the ROC curve analysis using the ipsilateral quantitative ADC values and found an area under the curve of 0.62, which indicates an insufficient accuracy to distinguish between TIA and stroke.

In patients in which the DWI was performed within 6 hours after symptom onset (8 TIA and 14 stroke patients), the area under the curve was 0.79 (95% CI: 0.58, 1.00; \( P = 0.04 \)) for \( r_{AI_{ADC}} \) and was 0.82 (95% CI: 0.65, 0.98; \( P = 0.01 \)) for \( r_{AI_{ADC}} \). The sensitivity and specificity of the \( r_{AI_{b=1000}} \) were 89% and 63% and were 71% and 67% for \( r_{AI_{ADC}} \).

**Discussion**

The main finding of our study was that even within 6 hours after symptom onset, patients with minor stroke and TIA could be differentiated by analyzing the signal intensity changes on DWI. To the best of our knowledge, this is the first report that demonstrates an increased signal intensity on the \( b=1000 \) image and a reduced intensity on the ADC maps in stroke patients as compared with TIA patients. Thirty-eight percent of the TIA patients within the first 6 hours after symptom onset and only 22% within 12 to 24 hours after symptom onset showed signal intensity changes. These results may be explained by the transient nature of DWI...
changes, probably caused by early reperfusion. This explanation supported by experimental studies reporting a rapid disappearance of DWI hyperintensity and ADC normalization in transient focal cerebral ischemia.\textsuperscript{15,16} Weber et al\textsuperscript{17} reported less abnormal ADC values in patients treated with recombinant tissue plasminogen activator (rtPA) compared with stroke patients without thrombolysis. In experimental stroke models, an ADC decrease during the first 28 hours after stroke onset was reported.\textsuperscript{18}

The incidence of DWI abnormalities in TIA patients (30\%) was comparable with the results of other investigations (21\% to 67\%).\textsuperscript{6–8,19,20} The lower incidence of DWI changes in our study compared with that of Rovira et al\textsuperscript{2} might be explained by a very strict definition of DWI abnormalities in our investigation. DWI abnormalities had to be confirmed by a corresponding ADC decrease and, in doubtful cases, additionally by a corresponding DWI change in a sagittal or coronal image. Crisostomo et al\textsuperscript{8} used similar MRI criteria and observed DWI changes in 21\% of their TIA patients. A short latency between onset of symptoms and DWI in our investigation compared with all other studies might also explain the lower incidence of DWI changes in our study. Li et al\textsuperscript{21} reported that after a 10- and 30-minute occlusion of the middle cerebral artery in rats, initial DWI hyperintensity disappeared soon after reperfusion. In the 30-minute group, delayed DWI changes occurred within 12 hours. Ringer et al\textsuperscript{21} described a recurrence of DWI abnormalities within 1 day after ischemia in an experimental stroke model.

Crisostomo et al\textsuperscript{8} described a patient with a pathological DWI and a TIA lasting only 40 seconds. They pointed out that the duration of symptoms is an inadequate determinant for having TIA or stroke. In our study population, we also observed a high variation of symptom duration. Because we found a similar incidence of DWI abnormalities in patients with TIA duration <1 hour and >1 hour, in our opinion, even the proposed new definition of TIA\textsuperscript{5} should be critically reviewed. As mentioned by Brown et al,\textsuperscript{22} we suggest that the definition of TIA remains a purely clinical one, but that the time from onset to complete resolution of symptoms and signs should be changed from 24 hours to 1 hour. Ballotta et al\textsuperscript{23} pointed out that in case of DWI changes, TIA should be termed “transient stroke.”

In our opinion, the results of our study are important for clinical practice because they describe the usefulness of analyzing the ratio of the average intensity on b=1000 and ADC images to differentiate between TIA and stroke, even within 6 hours after and during symptom onset. The predictive value of the rAI\textsubscript{b=1000} and rAI\textsubscript{ADC} was similar, with a trend toward a better discrimination between TIA and stroke using the rAI\textsubscript{ADC}. From a clinical point of view, we postulate that the rAI\textsubscript{b=1000} might be more useful because of a better contrast of the hyperintensity compared with normal brain. Another important finding of our study is the good discrimination accuracy between TIA and stroke by measuring the rAI. The area under the ROC curve was >0.8 and therefore implies good predictive power. Now, further prospective studies are necessary to verify and test the usefulness of these cutoff values to distinguish TIA and stroke.

In conclusion, we demonstrated that TIA and stroke can be differentiated even within 6 hours after symptom onset by analyzing the average signal intensity either on b=1000 or on ADC maps using DWI.

References
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