Incidence of New Diffusion-Weighted Imaging Lesions Outside the Area of Initial Hypoperfusion Within 1 Week After Acute Ischemic Stroke

Tatiana Usnich, MD; Fredrik N. Albach, MD; Peter Brunecker, Dr. rer. medic.; Jochen B. Fiebach, MD; Christian H. Nolte, MD

Background and Purpose—New diffusion-weighted imaging (DWI) lesions are common in patients with acute ischemic stroke. The pathophysiology of these new lesions is unclear. We differentiated new DWI lesions outside the area of initial hypoperfusion from those confined to the area of initial hypoperfusion.

Methods—Patients with acute stroke underwent 3 MRI examinations: on admission, on the next day, and 4 to 7 days after symptom onset. Patients were included if a perfusion deficit was present on the initial scan. Lesions on DWI images were delineated manually. Coregistered DWI images were analyzed visually for new hyperintensities. In reference to the perfusion maps (mean transit time), patients were classified as having “outside lesions” if new DWI lesions were outside or both outside and inside the area of the initial perfusion deficit or “inside lesions” if new DWI lesions were completely inside.

Results—We enrolled 164 patients. Thirty-eight patients (23%) had outside lesions and 34 patients (21%) had inside lesions. In multivariable regression analysis, new outside lesions were significantly associated with symptomatic carotid stenosis, multiple index lesions pattern, and high low-density lipoprotein levels. New inside lesions were significantly associated with (spontaneous or thrombolytic) vessel recanalization, multiple index lesions pattern, and low low-density lipoprotein levels.

Conclusion—Outside and inside lesions represent different pathophysiological entities. More specifically patients with outside lesions may have an increased risk for subsequent cerebrovascular events. (Stroke. 2012;43:2654-2658.)

Key Words: diffusion-weighted imaging ■ DWI ■ magnetic resonance imaging ■ new DWI lesion ■ perfusion imaging ■ silent stroke

New diffusion-weighted imaging (DWI) lesions are common in patients with acute ischemic stroke, especially within the first week after the index event. DWI lesions, even if clinically silent, are associated with higher risk of future strokes,1,2 cognitive decline, and depression.3,4 As previously described, approximately one fourth of patients develop new DWI lesions within the first week after the index event.5 However, the pathophysiology of these new DWI lesions remains unclear. Asdaghi and coworkers6 recently suggested that new DWI lesions are not de novo events, but rather are directly related to the original cerebrovascular syndrome. In which case it would be likely that new DWI lesions develop within the area of initial hypoperfusion. Another possibility is that these new DWI lesions are de novo events and could therefore express an increased risk of future strokes. In this case, they would be found outside or both outside and inside the area of initial hypoperfusion (outside lesions).

The aim of this study was to differentiate between these 2 new DWI lesion types, namely those that develop outside the area of initial hypoperfusion and those confined to the area of initial hypoperfusion only (inside lesions). Furthermore, we sought to determine which clinical characteristics are associated with the development of new outside lesions after ischemic stroke.

Methods

Patients

Patients were included in this study as part of an ongoing prospective observational study conducted by the Centre for Stroke Research Berlin at the Benjamin Franklin Campus of the Charité Hospital Berlin. The study enrolls all patients with an acute ischemic event within the last 24 hours who are eligible for MRI. Details of this study have been previously published.5,7 Patients recruited between March 2008 and March 2010, with a complete set of 3 examinations within the first week after symptom onset and an initial perfusion
deficit and MR angiography, were included in the final analysis. Patients who underwent endovascular interventions were excluded from the analysis. All patients received standard stroke unit care. The study was approved by the local Ethics Committee of Charité (EA4/026/08) and all patients gave written informed consent.

**Imaging Protocol**

The examinations were performed on a 3-T MRI scanner (Tim Trio; Siemens Medical, Erlangen, Germany). DWI was acquired with 230-mm field of view, 50 2.5-mm axial slices without extra gap, with one B0 and along 6 directions of $B=1000$ s/mm$^2$, TR/TE=7600/93 ms, and an acquisition matrix of 192x192. Other sequences included axial fluid-attenuated inversion recovery, T2*-weighted imaging, and 3-dimensional time-of-flight MR angiography of the intracranial circulation. Perfusion imaging was performed using dynamic susceptibility contrast and a fixed dosage of 5 mL Gadovist injection followed by 20 mL saline both at 5 mL/s. During injection, echoplanar gradient echo (T2*) images were acquired every 1.39 seconds for 118 seconds (TR/TE=1390/29 ms, 21 axial slices, thickness 5 mm, 0.5 mm extra gap per slice). We conducted 3 MR studies: on admission, on the next day, and 4 to 7 days after onset of symptoms.

**Image Analysis**

DWI were pseudonymized and afterward reviewed in random order by raters (F.N.A., T.U., J.B.F., C.H.N.) blinded to clinical information. Hyperintensities on initial DWI were delineated manually, coregistered to the DWI on second day, and resliced to 1-mm isotropic voxel size. Coregistered DWIs were analyzed visually for new hyperintensities separate from the index lesion through slice-by-slice comparison of the first and second as well as the second and third DWI. In this study, all new diffusion hyperintensities regardless of size and apparent diffusion coefficient value were considered.

The initial pattern of infarction was assessed on the second DWI. The presence of more than one diffusion lesion was described as a multiple index lesions pattern. Additionally, perfusion images from the first examination were reviewed. New DWI lesions were classified as being "outside lesions" if they were either outside or both outside and inside the area of initial perfusion deficit (see the Figure). New DWI lesion locations were classified as "inside lesions" if they were within the area of initial perfusion deficit.

**Clinical Data**

Sociodemographic and laboratory data were collected from the medical records. Symptomatic carotid stenosis was defined as stenosis >50% on color-coded duplex sonography or MR angiography that explained all the symptomatic lesions; occlusions were not considered. All patients were assessed for stroke severity directly before the first MRI examination and daily until the day of discharge by physicians certified to assess the National Institutes of Health Stroke Scale. A clinical stroke recurrence was defined as functional deterioration in the neurological status clearly distinct from that of the index stroke and attributable to vascular origin or a new sudden focal neurological deficit of vascular origin.

All patients were assessed 3 times daily for new neurological symptoms by a stroke physician dedicated to stroke care and patients' complaints were taken into account. At the time of follow-up clinical examination, physicians were blinded to MRI results.

Stroke subtype was classified according to the Trial of ORG 10172 in Acute Stroke Treatment criteria after a review of the clinical and imaging information. This was an observational study and secondary prevention measures were implemented according to current practice guidelines.

**Data Analysis**

Clinical and neuroradiological characteristics of patients were compared using the $\chi^2$ test for nominal and categorical variables. A multivariable logistic regression analysis was used to define factors associated with both new outside and inside lesions. Variables were included in the multivariable logistic regression models if univariate analysis suggested an association with $P<0.1$. In multivariable regression analysis, a significance threshold of $P<0.05$ was applied. Statistical analyses were performed using SPSS 19.0.

**Results**

The study population consisted of 164 patients with a perfusion deficit on the initial scan (39% female; median age, 71 years [interquartile range, 62–79]; median National Institutes of Health Stroke Scale 4 [interquartile range, 3–8]). Sociodemographic and clinical data are shown in Table 1. The median time from symptom onset to first, second, and third MRI was 5 hours (interquartile range, 2–16), 29 hours (interquartile range, 24–41), and 118 hours (interquartile range, 105–137), respectively. Clinical stroke recurrence occurred in 2.4% (N=4) of patients within the first week.

New DWI lesions were detected in 72 (44%) patients during the first week after stroke, of which 38 had outside...
lesions (53%) and 34 had inside lesions (47%). Ninety-two patients (56%) had no new DWI lesions.

Patients with outside lesions, inside lesions, and no lesions differed significantly in the presence of atrial fibrillation and multiple index lesions pattern (both more often in patients with any new DWI lesions), presence of symptomatic carotid stenosis, and low-density lipoprotein (LDL) >130 mg/dL (both more often in patients with outside lesions), thrombolysis, and vessel recanalization (both more often in patients with inside lesions; Table 1).

In multivariable regression analyses, multiple index lesions pattern, symptomatic carotid stenosis, and high LDL levels were independently associated with new outside lesions. Multiple index lesions pattern, vessel recanalization, and low LDL levels (<130 mg/dL) were significantly associated with new inside lesions (Table 2).

Moreover, 64 patients had received 3 scans but had not shown an initial perfusion deficit. These patients were excluded from the final analysis because the distinction between inside and outside lesions was not possible. Of these patients, 10 (16% of 64) had new DWI lesions.

**Discussion**

Similar to previous reports, we observed new DWI lesions within the first week after the ischemic event in 44% of patients included in this study. In an effort to better understand the pathophysiology of these new lesions, we differentiated between 2 types of new DWI lesions, namely, lesions evolving outside (or both outside and inside) of the area of initial hypoperfusion and lesions evolving only inside. More patients displayed new outside lesions (53%) than new inside lesions (47%).

Comparison between patients without new lesions and with outside lesions and inside lesions revealed several differences. Multivariable logistic regression analyses revealed a significant association of outside lesions with symptomatic carotid stenosis, multiple index lesions pattern, and high LDL levels (>130 mg/dL). On the other hand, inside lesions were associated with vessel recanalization, multiple index lesions pattern, and low LDL levels.

Based on these results, we argue against the notion of a common etiology of both lesion types. The strong association

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### Table 1. Sociodemographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Inside Lesions (N = 34)</th>
<th>Outside Lesions (N = 38)</th>
<th>No New Lesions (N = 92)</th>
<th>Any Lesions (N = 72)</th>
<th>P Value</th>
<th>Any Lesions (N = 72)</th>
<th>No New Lesions (N = 92)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, female</strong></td>
<td>11 (32.4%)</td>
<td>16 (42.1%)</td>
<td>37 (40.2%)</td>
<td>0.656</td>
<td>27 (37.5%)</td>
<td>37 (40.2%)</td>
<td>0.723</td>
<td></td>
</tr>
<tr>
<td><strong>Age &gt;70 y</strong></td>
<td>21 (61.8%)</td>
<td>21 (55.3%)</td>
<td>50 (54.3%)</td>
<td>0.568</td>
<td>42 (58.3%)</td>
<td>50 (54.3%)</td>
<td>0.610</td>
<td></td>
</tr>
<tr>
<td><strong>NIHSS, &gt;3</strong></td>
<td>22 (64.7%)</td>
<td>21 (55.3%)</td>
<td>52 (65.6%)</td>
<td>0.662</td>
<td>43 (59.7%)</td>
<td>52 (56.5%)</td>
<td>0.680</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>9 (26.5%)</td>
<td>8 (21.1%)</td>
<td>23 (25.0%)</td>
<td>0.849</td>
<td>17 (23.6%)</td>
<td>23 (25.0%)</td>
<td>0.837</td>
<td></td>
</tr>
<tr>
<td><strong>Arterial hypertension</strong></td>
<td>26 (76.5%)</td>
<td>31 (81.6%)</td>
<td>71 (77.2%)</td>
<td>0.832</td>
<td>57 (79.2%)</td>
<td>71 (77.2%)</td>
<td>0.760</td>
<td></td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>14 (41.2%)</td>
<td>12 (31.6%)</td>
<td>19 (20.7%)</td>
<td>0.058</td>
<td>26 (36.1%)</td>
<td>19 (20.7%)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td><strong>TOAST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Large artery</td>
<td>12 (35.3%)</td>
<td>16 (42.1%)</td>
<td>31 (33.7%)</td>
<td>28 (38.9%)</td>
<td>31 (33.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>10 (29.4%)</td>
<td>11 (28.9%)</td>
<td>23 (25.0%)</td>
<td>21 (29.2%)</td>
<td>23 (25.0%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Small vessel stroke</td>
<td>0</td>
<td>0</td>
<td>16 (17.4%)</td>
<td>0</td>
<td>16 (17.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other determined</td>
<td>1 (2.9%)</td>
<td>1 (2.6%)</td>
<td>2 (2.2%)</td>
<td>2 (2.8%)</td>
<td>2 (2.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>11 (32.4%)</td>
<td>10 (26.3%)</td>
<td>20 (21.7%)</td>
<td>21 (29.2%)</td>
<td>20 (21.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombotic therapy</td>
<td>8 (23.5%)</td>
<td>15 (39.5%)</td>
<td>32 (34.8%)</td>
<td>0.334</td>
<td>23 (31.9%)</td>
<td>32 (34.8%)</td>
<td>0.702</td>
<td></td>
</tr>
<tr>
<td>Double antithrombotic</td>
<td>1 (2.9%)</td>
<td>0</td>
<td>4 (4.3%)</td>
<td>0.423</td>
<td>1 (1.4%)</td>
<td>4 (4.3%)</td>
<td>0.274</td>
<td></td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>2 (5.9%)</td>
<td>4 (10.5%)</td>
<td>7 (7.6%)</td>
<td>0.756</td>
<td>6 (8.3%)</td>
<td>7 (7.6%)</td>
<td>0.865</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>6 (17.6%)</td>
<td>3 (7.9%)</td>
<td>15 (16.3%)</td>
<td>0.400</td>
<td>9 (12.5%)</td>
<td>15 (16.3%)</td>
<td>0.494</td>
<td></td>
</tr>
<tr>
<td>PAOD</td>
<td>1 (2.9%)</td>
<td>3 (7.9%)</td>
<td>7 (7.6%)</td>
<td>0.614</td>
<td>4 (5.6%)</td>
<td>7 (7.6%)</td>
<td>0.602</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>8 (23.5%)</td>
<td>13 (34.2%)</td>
<td>27 (29.3%)</td>
<td>0.610</td>
<td>21 (29.2%)</td>
<td>27 (29.3%)</td>
<td>0.980</td>
<td></td>
</tr>
<tr>
<td>Symptomatic carotid stenosis</td>
<td>1 (2.9%)</td>
<td>7 (18.4%)</td>
<td>5 (5.4%)</td>
<td>0.022</td>
<td>8 (11.1%)</td>
<td>5 (5.4%)</td>
<td>0.182</td>
<td></td>
</tr>
<tr>
<td>Multiple index lesions</td>
<td>32 (94.1%)</td>
<td>34 (89.5%)</td>
<td>50 (54.3%)</td>
<td>0.000</td>
<td>66 (91.7%)</td>
<td>50 (54.3%)</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Thrombolyis</td>
<td>17 (50.0%)</td>
<td>9 (23.7%)</td>
<td>16 (17.4%)</td>
<td>0.001</td>
<td>26 (36.1%)</td>
<td>16 (17.4%)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Vessel recanalization</td>
<td>21 (61.8%)</td>
<td>8 (21.1%)</td>
<td>10 (10.9%)</td>
<td>0.000</td>
<td>29 (40.3%)</td>
<td>10 (10.9%)</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Glucose, &gt;180 mg/dL</td>
<td>4 (12.5%)</td>
<td>4 (11.1%)</td>
<td>14 (15.6%)</td>
<td>0.782</td>
<td>8 (11.8%)</td>
<td>14 (15.6%)</td>
<td>0.496</td>
<td></td>
</tr>
<tr>
<td>LDL, &gt;126 mg/dL</td>
<td>13 (40.6%)</td>
<td>18 (50.0%)</td>
<td>37 (41.1%)</td>
<td>0.630</td>
<td>31 (45.6%)</td>
<td>37 (41.1%)</td>
<td>0.574</td>
<td></td>
</tr>
<tr>
<td>LDL, &gt;130 mg/dL</td>
<td>4 (12.1%)</td>
<td>18 (47.4%)</td>
<td>26 (29.5%)</td>
<td>0.005</td>
<td>22 (31.0%)</td>
<td>26 (29.5%)</td>
<td>0.844</td>
<td></td>
</tr>
<tr>
<td>INR &gt;2</td>
<td>2 (5.9%)</td>
<td>2 (5.3%)</td>
<td>4 (4.3%)</td>
<td>0.932</td>
<td>4 (5.6%)</td>
<td>4 (4.3%)</td>
<td>0.722</td>
<td></td>
</tr>
<tr>
<td>&gt;1.7</td>
<td>2 (5.9%)</td>
<td>2 (5.3%)</td>
<td>6 (6.5%)</td>
<td>0.962</td>
<td>4 (5.6%)</td>
<td>6 (6.5%)</td>
<td>0.797</td>
<td></td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; CHD, coronary heart disease; PAOD, peripheral artery occlusive disease; LDL, low-density lipoprotein; INR, international normalized ratio.

*The variable glucose was known in 33/36/90 patients, respectively.

† The variable LDL was known in 34/38/88 patients, respectively.
of inside lesions with (spontaneous or postthrombolytic) vessel recanalization supports the assumption that new lesions are most likely related to the completion of the natural history of the original cerebrovascular syndrome. In other words, new inside lesions may result from incomplete clot dissolution causing new (smaller) occlusions within the vessel supply territory. Alternatively, appearance of new inside lesions may depend on the severity of baseline hypoperfusion. Bang et al\textsuperscript{11} reported the appearance of new inside lesions within an area of mild initial hypoperfusion as opposed to infarct growth within an area of severe initial hypoperfusion. Still, recanalization often occurs without evidence of new lesions and might be associated with a better prognosis.

It is interesting, however, that a large proportion of new lesions evolve outside of the area of initial hypoperfusion. The incidence of outside lesions is similar to findings of Kang et al\textsuperscript{2} but higher in our study than reported in a previous, smaller study that included less severely affected patients as well as patients with transient ischemic attack.\textsuperscript{6,9} Our larger sample size allowed for an adjusted multivariable analysis that revealed the strong association of outside lesions with symptomatic carotid stenosis. Symptomatic carotid stenosis is a well-known risk factor for early stroke recurrence.\textsuperscript{12} Carotid stenosis was not associated with new inside lesions.

It is well known that high LDL levels are associated with atherosclerosis, which further supports our hypothesis that patients with outside lesions are at higher risk for stroke recurrence. However, information about use of HMG-CoA reductase inhibitors or levels of other lipoproteins was not considered and should be adjusted for in future analyses.

Several studies have also reported an association between new DWI lesions and multiple index lesions pattern.\textsuperscript{1,5,9} Multiple index lesions pattern has also been linked to a higher risk of subsequent clinical events.\textsuperscript{13}

The significance of new DWI lesions without neurological deficit remains unclear. There is growing evidence that the ischemia underlying even transient DWI lesions is leaving permanent tissue damage. Research in rats found that after 20 minutes middle cerebral artery occlusion, behavioral and histological anomalies remained although MRI parameters recovered.\textsuperscript{14} In another study, histological examinations demonstrated neuronal necrosis both after transient and permanent recovery of DWI lesions after temporary middle cerebral artery occlusion; only the number of necrotic neurons differed between groups.\textsuperscript{15} Although one should be cautious when interpreting animal studies with regard to patient analyses, these results further support the hypothesis that DWI lesions are not only associated with higher risk of future strokes,\textsuperscript{1,2} cognitive decline, and depression,\textsuperscript{3,4} but are also associated with permanent neuronal necrosis.

This study has limitations. Patients were only included in this study after giving written informed consent. Therefore, severely affected patients incapable of providing consent are underrepresented. Furthermore, this is a single-center study. Thus, the results of this study cannot be generalized to all patients with stroke. Multicenter trials with larger cohorts and different study populations are warranted. However, to the best of our knowledge, this is the largest study to investigate new DWI lesions after ischemic stroke in patients recruited in a consecutive, prospective manner as of yet.

In conclusion, new outside and inside lesions have distinct underlying pathophysiological mechanisms and should therefore be differentiated in the clinical setting. The development of outside lesions cannot be explained by the natural course of the original cerebrovascular syndrome. Therefore, these patients may represent a subset of patients with a higher risk for subsequent manifest stroke.

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**Disclosures**

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**References**


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