Clinical and Radiological Courses Do Not Differ Between Fluid-Attenuated Inversion Recovery-Positive and Negative Patients With Stroke After Thrombolysis

Martin Ebinger, MD, PhD; Ann-Christin Ostwaldt; Ivana Galinovic, MD, MSc; Michal Rozanski, MD; Peter Brunecker, MD; Christian H. Nolte, MD; Matthias Endres, MD; Jochen B. Fiebach, MD

Background and Purpose—After acute ischemic stroke, the proportion of patients with detectable lesions on fluid-attenuated inversion recovery (FLAIR) MRI sequences increases over time. We investigated whether thrombolysis was less effective in FLAIR-positive versus -negative patients.

Methods—In this single-center hospital-based study, all consecutive patients with ischemic stroke who underwent an MRI before and 24 hours after thrombolysis between May 2008 and October 2009 were included. Patients were included if exact time of onset was known and thrombolysis was performed within 3 hours up until August 2008 and within 4.5 hours from September 2008 on. Blinded to time of symptom onset, 3 raters independently judged the visibility of lesions on FLAIR. Lesion volumes on diffusion-weighted imaging as well as National Institutes of Health Stroke Scale before and 1 day after thrombolysis were determined.

Results—Of 51 patients (25 females, mean age 71, median National Institutes of Health Stroke Scale 6), 26 were FLAIR-positive. Neither lesion growth nor change in National Institutes of Health Stroke Scale differed significantly between FLAIR-positive versus -negative patients: median growth 2.6 mL (interquartile growth, −0.1 to 17.6) versus 0.8 mL (interquartile range, 0.1 to 17.8) and change in National Institutes of Health Stroke Scale −2.5 (interquartile range, −5 to 0) versus −2.0 (interquartile range, −5 to 0.5), respectively (P > 0.5, Mann–Whitney rank sum test).

Conclusion—Visibility of lesions on FLAIR in areas of diffusion restriction was not predictive of the response to thrombolysis. (Stroke. 2010;41:00-00.)

Key Words: acute stroke ■ MRI ■ thrombolysis

Currently, patients with acute ischemic stroke are eligible for thrombolysis within 4.5 hours after symptom onset. After vessel occlusion, cell death cascades evolve in a time-dependent manner and lead to the conversion of an ischemic penumbra into the infarcted brain tissue. However, the dynamics of lesion growth differ significantly between individual patients with stroke. Therefore, tissue signatures determined by MRI rather than time from symptom onset may be a better criterion of a stage in which treatment is no longer effective or may even become harmful. Previous studies have shown that hyperintensities on fluid-attenuated inversion recovery (FLAIR) correlate to a certain extent with time from symptom onset. However, no study has investigated if the effects of thrombolysis on lesion growth and neurological deficits differ depending on FLAIR lesion visibility before treatment.

We hypothesized that patients with visible lesions on FLAIR in the area of diffusion restriction show significantly different responses in terms of clinical improvement and lesion growth after thrombolysis as compared with patients without visible lesions on FLAIR.

Methods

Details of the imaging protocol have been reported previously. All consecutive patients with stroke who underwent a 3-T MRI before and 24 hours after thrombolysis between May 2008 and October 2009 were included if exact time of onset was known. Until August 2008, thrombolysis was performed within 3 hours postsymptom onset. Thereafter, the time window was extended to 4.5 hours because of the results of European Cooperative Acute Stroke Study (ECASS) 3. Thrombolysis was performed regardless of lesion visibility on FLAIR. Blinded to time of symptom onset, 3 raters independently judged the visibility of lesions on FLAIR in the area of diffusion restriction on the scans of Day 1. In cases of disagreement, consensus was achieved during a joint second reading. If patients had severe white matter damage or no consensus could be reached for other reasons, patients were
Lesion volumes on diffusion-weighted imaging as well as National Institutes of Health Stroke Scale (NIHSS) before (Day 1) and 1 day after thrombolysis (Day 2) were determined. A group comparison of FLAIR-positive and FLAIR-negative patients in terms of diffusion-weighted imaging lesion volume growth (volume Day 2 / volume Day 1) and clinical outcome (NIHSS on Day 2 / NIHSS on Day 1) was performed using a nonparametric test. Lesion volumes were delineated manually on each slice using MRIcro (Version 1.40). The program summed up all pixels within the delineated region of interest. The total number of pixels was then multiplied by the size of the voxels, including interslice gaps, to obtain the lesion volume. All analyses were performed with PASW Statistics 18.

Results

We identified 61 patients who fulfilled our inclusion criteria. Ten patients were excluded from further analyses due to poor imaging quality (3) or inability to reach consensus, for example, due to severe leukoaraiosis in the area of the diffusion restriction (7). Median baseline NIHSS of the remaining 51 patients (25 females, mean age 71 years, median time to first scan 82 minutes, interquartile range [IQR] 69 to 106 minutes) was 6 (IQR 4 to 11) and median lesion volume was 2.8 mL (IQR 0.6 to 8.1). Follow-up MRI and NIHSS were performed on Day 2 in 45 patients and on Day 3, 5, 6, or 9 in 6 patients due to logistical problems or patients’ inability to undergo scanning at an earlier point in time. We found 26 FLAIR-positive and 25 FLAIR-negative patients. Baseline characteristics did not differ significantly between the groups (Table).

We found no significant difference in terms of lesion growth between FLAIR-positive (median growth 2.6 mL, IQR -0.1 to 17.6) and FLAIR-negative (median growth 0.8 mL, IQR 0.1 to 17.8) patients (P=0.792, Mann–Whitney rank sum test; Figure). Five patients (3 FLAIR-positive and 2 FLAIR-negative patients) showed shrinkage of diffusion-weighted imaging lesion volume by >0.5 mL (median diffusion-weighted imaging shrinkage -2.5 mL). Median change NIHSS 1 day after thrombolysis did not differ significantly between groups (FLAIR-positive: -3, IQR -5 to 0 versus FLAIR negative: -2, IQR -5 to 1; P=0.603, Mann–Whitney rank sum test).

Discussion

Based on our results, we rejected our hypothesis. We found no significant difference in terms of lesion growth or neurological changes after thrombolysis between FLAIR-positive and FLAIR-negative patients. Therefore, thrombolysis should not be withheld solely based on FLAIR lesion visibility. Within the current time window for thrombolysis, it is not uncommon to detect lesions on FLAIR in the area of diffusion restriction. In our sample, approximately 50% of patients were FLAIR-positive, similar to previously reported results.2,3

An acknowledged limitation of our study is a relatively small sample size with a wide range of lesion volumes yielding the possibility of a Type II error. We may have failed to observe a possibly existing difference between FLAIR-positive and FLAIR-negative patients due to our sample size. In other words, absence of evidence is not evidence of absence5 and larger studies on this topic may be warranted.

Table. Baseline Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>FLAIR-Positive (n=26)</th>
<th>FLAIR-Negative (n=25)</th>
<th>P (for t Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72 (SD 12.8)</td>
<td>69 (SD 13.3)</td>
<td>0.798</td>
</tr>
<tr>
<td>Females, No.</td>
<td>12 (46%)</td>
<td>13 (52%)</td>
<td>0.807</td>
</tr>
<tr>
<td>NIHSS Day1</td>
<td>8 (IQR 4–16)</td>
<td>6 (IQR 4–11)</td>
<td>0.106</td>
</tr>
<tr>
<td>Time to MRI, minutes</td>
<td>86 (IQR 67–105)</td>
<td>81 (IQR 69–108)</td>
<td>0.774</td>
</tr>
<tr>
<td>Diffusion-weighted imaging lesion volume Day 1, mL</td>
<td>4.1 (IQR 1.7–9.2)</td>
<td>1.4 (IQR 0.6–8.1)</td>
<td>0.306</td>
</tr>
</tbody>
</table>

*There were no significant differences of baseline characteristics between 51 FLAIR-positive and -negative patients.

Figure. Similar lesion growth in 2 patients with stroke. Patient A is FLAIR-positive on Day 1 (A2) and shows a right parietal lesion on diffusion-weighted imaging (DWI) Day 1 (A1) and Day 2 (A3). Patient B is FLAIR-negative on Day 1 (B2) and shows a left insular lesion on DWI Day 1 (B1) and Day 2 (B3).
Nevertheless, at this point in time, patients with ischemic stroke should be regarded as eligible for thrombolysis within 4.5 hours after symptom onset independent of FLAIR lesion visibility.

**Sources of Funding**
The research leading to these results has received funding from the Federal Ministry of Education and Research through the Grant Center for Stroke Research Berlin (01 EO 0801), the Volkswagen Foundation (Lichtenberg program to M. Endres), DFG (NeuroCure, Exc 257), and EU (European Stroke Network).

**Disclosures**
M. Endres received research grants from AstraZeneca (significant), and lecture fees from Boehringer, Sanofi, AstraZeneca, Bayer, Novartis, Tromssdorff, BerlinChemie, and GSK (all moderate). There are no other conflicts to report.

**References**
Clinical and Radiological Courses Do Not Differ Between Fluid-Attenuated Inversion Recovery-Positive and Negative Patients With Stroke After Thrombolysis

Martin Ebinger, Ann-Christin Ostwaldt, Ivana Galinovic, Michal Rozanski, Peter Brunecker, Christian H. Nolte, Matthias Endres and Jochen B. Fiebach

Stroke. published online July 1, 2010;

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/early/2010/07/01/STROKEAHA.110.583971.citation

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/