Background and Purpose—We investigated if hyperintensities on fluid-attenuated inversion recovery (FLAIR) sequences in arteries and parenchyma are associated with poor outcome 3 months after thrombolysis.

Methods—Consecutive acute stroke patients with known time of symptom onset who had an MRI before and 1 day after thrombolysis were included in this study. Blinded to follow-up imaging and outcome, 2 raters independently judged the presence or absence of arterial and parenchymal FLAIR hyperintensities. Functional outcome (modified Rankin Scale) was assessed after 3 months.

Results—Out of 90 patients, 22 had parenchymal FLAIR hyperintensities and 42 had hyperintense vessels. The combination of FLAIR hyperintensities in arteries and parenchyma occurred in 15 patients. Stepwise forward regression analysis revealed an adjusted odds ratio of 14.5 for a worse outcome (modified Rankin Scale score ≥2) in patients with FLAIR hyperintensities in arteries and parenchyma (95% confidence interval, 1.3–158.5; P=0.03).

Conclusions—FLAIR hyperintensities in arteries and parenchyma are an easy-to-use MRI feature in acute ischemic stroke associated with poor outcome 3 months after thrombolysis. (Stroke. 2012;43:539-542.)

Key Words: acute stroke ■ magnetic resonance imaging ■ thrombolysis

Fluid-attenuated inversion recovery (FLAIR) sequences without hyperintensities in the area of diffusion restriction are a good indicator of a stroke within 4.5 hours from symptom onset. It is unclear whether FLAIR status influences outcome after thrombolysis. Apart from hyperintensities in the area of diffusion restriction, hyperintense vessels are also commonly found on FLAIR images of acute ischemic stroke patients. They have been interpreted as an indicator of slow blood flow, inadequate collateral circulation, and poor outcome. Others found no independent association of hyperintense vessels with clinical outcomes.

The ischemic cascade is an intricate process involving complex hemodynamics and a series of biochemical reactions on a cellular level. MRI potentially offers an approach to both sides of this medal in a single sequence, namely FLAIR. We investigated if FLAIR hyperintensities in arteries and parenchyma are associated with worse outcome 3 months after thrombolysis.

Patients and Methods

This is a substudy of the 1000+ study, registered with clinicaltrials.gov (NCT 00715533). Between May 2008 and May 2010, consecutive acute stroke patients with known time of onset who had an MRI before and 1 day after thrombolysis were included after informed consent. All patients received thrombolysis within 4.5 hours.

Procedures

Blinded to follow-up imaging and outcome, 2 raters (M. Ebinger, A.K.) independently judged the presence or absence of parenchymal FLAIR hyperintensities in the area of diffusion restriction (FLAIR hyperintensities in parenchyma, FHP) and arterial FLAIR hyperintensities in vessels that were not considered the main occluded vessel ipsilateral to the diffusion restriction (FHA). In case of disagreement, the raters met for a consensus. Patients were then allocated to the following 3 FLAIR categories: (1) no FHA and no FHP; (2) either FHA or FHP; and (3) FLAIR hyperintensities in arteries and parenchyma (FRAP; Figure). For functional outcome including mortality, we assessed the modified Rankin Scale (mRS) score after 3 months.

Statistics

After univariate analysis comparing baseline characteristics between patients with mRS score 0 to 2 to patients with mRS score ≥2, all significant parameters and the 3-level categorical FLAIR variables were included in a binary logistic regression using a stepwise forward regression analysis to identify predictors of outcome. All statistical analyses were performed using SPSS version 19.

Results

Baseline Characteristics

Out of 90 patients (44 female; median age, 72 years, interquartile range [IQR], 65–81 years), 22 patients had FHP by guest on June 26, 2017 http://stroke.ahajournals.org/ Downloaded from
and 42 patients had FHA. Inter-rater agreements for FHP and FHA were high ($\kappa=0.81$ and 0.85; $P<0.001$). Table 1 shows baseline characteristics.

FHP
Mortality rates differed significantly between patients with FHP and those without (21% versus 4.5%; $P=0.04$). Good functional outcome occurred more often in patients without FHP (63.6% versus 31.6%; $P=0.018$). Chances of good outcome were significantly reduced in FHP (relative risk reduction, 50.3%). FHP was associated with male gender (73% versus 44%; $P=0.03$), FHA (68% versus 40%; $P=0.03$), and a higher median diffusion-weighted imaging lesion volume (4.1 mL; IQR, 1.3–17.5 versus 0.1–4.1; $P<0.01$). In secondary analyses, median absolute growth in patients without FHP was 0.5 mL (IQR, 0.0–6.2) versus 2.6 mL (IQR, 1.1–27.8; $P=0.048$) in FHP. Median relative growth was 1.8 (IQR, 1.0–4.0) versus 2.1 (IQR, 1.7–3.6; $P=0.496$), and median change in NIHSS score (relative risk reduction, 44.1%). FHA was associated with FHP (36% versus 15%; $P=0.03$), atrial fibrillation (41% versus 20%; $P=0.03$), arterial occlusion (85% versus 21%; $P<0.01$), higher median NIHSS score (10 versus 5; IQR, 4–8; $P<0.01$), higher median diffusion-weighted imaging lesion volume (5 mL; IQR, 1.0–18.9 versus 0.1–17.7; $P<0.01$), and higher median volume of perfusion deficits (72.5 mL versus 3.27 mL; IQR, 22.5–139.8 versus 0.9–19.4; $P<0.01$). Rates of a 75% reperfusion on day 2 did not differ between patients with and without FHA (39% versus 36%; $P=0.8$). In secondary analyses, median absolute growth in patients without FHA was 0.3 mL (IQR, 0.0–2.1) versus 3.7 mL (0.7–28.2; $P=0.000$) in FHA; median relative growth was 2.1 (IQR, 0.9–4.0) versus 1.8 (IQR, 1.4–4.5; $P=0.781$), and median change in NIHSS was $-0.8$ (IQR, 3 to 0) versus $-2$ (IQR, 1.0–4.0; $P=0.658$), respectively.

FHA
Mortality rates did not differ significantly between patients with FHA and those without (8.3% versus 8.1%). Good functional outcome occurred after 3 months occurred more often in patients without FHA (69% versus 41%; $P=0.02$); chances of good outcome were significantly reduced in FHA (relative risk reduction, 44.1%). FHA was associated with FHP (36% versus 15%; $P=0.03$), perfusion-diffusion mismatch (76% versus 46%; $P<0.01$), arterial occlusion (85% versus 21%; $P<0.01$), higher median NIHSS score (10 versus 5; IQR, 4–8; $P<0.01$), higher median diffusion-weighted imaging lesion volume (5 mL; IQR, 1.0–18.9 versus 0.1–17.7; $P<0.01$), and higher median volume of perfusion deficits (72.5 mL versus 3.27 mL; IQR, 22.5–139.8 versus 0.9–19.4; $P<0.01$). Rates of a 75% reperfusion on day 2 did not differ between patients with and without FHA (39% versus 36%; $P=0.8$). In secondary analyses, median absolute growth in patients without FHA was 0.3 mL (IQR, 0.0–2.1) versus 3.7 mL (0.7–28.2; $P=0.000$) in FHA; median relative growth was 2.1 (IQR, 0.9–4.0) versus 1.8 (IQR, 1.4–4.5; $P=0.781$), and median change in NIHSS was $-0.8$ (IQR, 3 to 0) versus $-2$ (IQR, 1.0–4.0; $P=0.658$), respectively.

FRAP
Mortality rates did not differ significantly between the 3 FLAIR categories of patients (5%, 9%, and 17%, respectively; $P=0.3$). Good functional outcome occurred in 73% (n=30) of the patients without hyperintensities; patients with 1 hyperintensity sign on FLAIR achieved good functional outcome in 47% (n=15); only 25% (n=3) of patients with FRAP had a good functional outcome (2-sided Fischer exact test; $P<0.01$). Chances of good outcome were significantly reduced in patients with FRAP (relative risk reduction, 65.9%). Rate of reperfusion did not differ significantly between the 3 groups (42%, 23%, and 55%, respectively; $P=0.2$). In a Fisher exact test, unadjusted odds ratios for bad outcome were 3.09 (95% confidence interval [CI], 1.16–8.23; $P=0.030$) for the category 1 hyperintensity and 8.23 (95% CI, 1.87–35.87; $P=0.005$) for FRAP in comparison to the reference category (no hyperintensities). In univariate analyses comparing patients with good (mRS score 0–2) and bad outcomes (mRS score >2) that included all baseline parameters listed in Table 1, female gender, hypertension, NIHSS score, volumes of diffusion-weighted imaging lesion, and perfusion deficit turned out to be significantly different between both groups. The results of a binary regression that included these 5 parameters along with the 3-level categorical FLAIR variable are shown in Table 2. In secondary analyses, median absolute growth in patients without FRAP was 0.7
Forward Variable Selection

Table 2. Final Model for the Binary Regression With Stepwise Forward Variable Selection

<table>
<thead>
<tr>
<th></th>
<th>OR for mRS Score &gt;2</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>10.89</td>
<td>1.86–63.77</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.04</td>
<td>0.003–0.50</td>
<td>0.012</td>
</tr>
<tr>
<td>NIHSS (per 1 point increase)</td>
<td>1.3</td>
<td>1.08–1.57</td>
<td>0.005</td>
</tr>
<tr>
<td>One-FLAIR hyperintensity</td>
<td>6.21</td>
<td>1.05–36.65</td>
<td>0.044</td>
</tr>
<tr>
<td>FRAP</td>
<td>14.45</td>
<td>1.32–158.51</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Candidates were all parameters that turned out significantly different between patients with good (mRS score 0–2) and bad outcomes (mRS score >2) in univariate analysis. Volumes of diffusion-weighted imaging lesion and perfusion deficit were significant in the univariate analysis; in the binary regression, they did not turn out to be relevant and therefore fell out of the model.

CI indicates confidence interval; FLAIR, fluid-attenuated inversion recovery; FRAP, FLAIR hyperintensities in arteries and parenchyma; mRS, modified Rankin Scale; OR, odds ratio.

Discussion

For the first time to our knowledge, we show that parenchymal and arterial FLAIR hyperintensities are associated with poor outcome 3 months after thrombolysis. The combination of these signs, ie, the FRAP sign, seems to increase this separation effect further.

Similar to our previous findings, we observed no significant difference between patients with and without FHP in terms of time-to-scan and no significant difference in subacute change of NIHSS score between patients with or without any of the FLAIR signs mentioned. In a further study, we scanned within 12 hours from symptom onset and found a time difference of ~90 minutes between patients with FHP and those without it. In other words, FHP might be a good differentiator between time of onset before or after 4.5 hours, but we were not able to reliably allocate patients to smaller time windows within 4.5 hours using signal intensity on FLAIR. Differing absolute growth between groups was attributable to baseline differences of lesion volumes because relative growth was similar. Compared to our previous work, we here present results from a larger cohort using a more widely accepted outcome measure (mRS score after 3 months) and a new combination of 2 FLAIR features (FRAP).

The pathophysiological mechanisms underlying FRAP are not yet fully understood. FHP might be attributed to a net increase of water and associated with a higher likelihood to be beyond the current time window for thrombolysis. It may be a marker of more severe ischemia within 4.5 hours. This hypothesis should be addressed in future research, eg, comparing times until affected parenchyma turns hyperintense on FLAIR between patients with good and bad collateral status and identical arterial occlusions. FHA is most likely attributable to slow blood flow. It has been suggested as an indicator of both collateral blood flow and bad outcome after 1 month. FHA may be testimony for impaired hemodynamics and inefficient collaterals. Conflicting findings from previous studies may be partly attributable to differing methodologies. For instance, Schelling et al found no association between MRI vessel signs and outcome in 56 patients treated within 3 hours. They used a variety of early vessel signs, including hyperintensities on FLAIR at the site...
of arterial obstruction; patients who had FHP did not receive thrombolysis in that study. In contrast, we defined FHA as hyperintensities in vessels that were not considered the main occluded vessel; we thrombolysed stroke patients within 4.5 hours of symptom onset independent of FHP.

With relatively low numbers, our study bears the risk of type I and II errors. The use of a stepwise forward regression analysis only partially meets this concern. The statistical instability that comes with low numbers remains a limitation of this study. However, our results can be interpreted as a strong foundation to generate the hypothesis that FRAP might be an excellent predictor of functional outcome in stroke patients who receive thrombolysis within 4.5 hours of symptom onset. Because this is not a prospective placebo-controlled trial, our results do not qualify the FRAP sign as an exclusion criterion when considering thrombolysis. However, depending on further validation of the FRAP sign in a separate dataset, this easy-to-use MRI feature may be helpful to enrich study cohorts in terms of patients likely to benefit from tissue-type plasminogen activator or possibly other recanalizing drugs or devices.

Acknowledgments
The authors thank Sebastian Dörken for help with the Figure.

Sources of Funding
The research leading to these results has received funding from the Federal Ministry of Education and Research via the grants from the Center for Stroke Research Berlin (01 EO 0801), from the Volkswagen Foundation (Lichtenberg program to Matthias Endres), from the EU (EuStroke, ARISE), and from the German Research Foundation (NeuroCure, SFB-TR 43).

Disclosures
M. Ebinger, A.K., P.B., I.G., and U.M. have no conflicts of interests to report. M. Endres reports consultancies, grants, and/or payments for lectures including service on speakers bureaus for/from the following: Astra Zeneca, Bayer, Berlin Chemie, BMS, Boehringer-Ingelheim, Glaxo Smith Kline, Novartis, Pfizer, Sanofi-Aventis, and Trommsdorff. He holds a patent for the upregulation of type III endothelial cell nitric oxide synthase by HMG-CoA reductase inhibitors (U.S. patent number 6,147,109). J.B.F. reports board memberships, consultancies, and/or payments for lectures including service on speakers’ bureaus for/from the following: Boehringer-Ingelheim, Lundbeck, Siemens, Sygnis, and Synarc. C.H.N. reports consulting fee/honorarium and travel/accommodations/meeting expenses paid by Boehringer-Ingelheim, and a payment for development of educational presentations by TAKEDA.

References
Fluid-Attenuated Inversion Recovery Images and Stroke Outcome After Thrombolysis

Martin Ebinger, Anna Kufner, Ivana Galinovic, Peter Brunecker, Uwe Malzahn, Christian H. Nolte, Matthias Endres and Jochen B. Fiebach

Stroke. 2012;43:539-542; originally published online October 27, 2011;
doi: 10.1161/STROKEAHA.111.632026

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 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/43/2/539

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/