Fluid-Attenuated Inversion Recovery Images and Stroke Outcome After Thrombolysis

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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

Patients
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.
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 (mRS score 0–2) 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 versus 0.8 mL; IQR, 1.3–17.5 versus IQR, 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, 1.0–6.2; $P=0.496$), and median change in National Institutes of Health Stroke Scale (NIHSS; score day 2 minus score day 1) was $-3$ (IQR, $-5$ to 0) versus $-1$ (IQR, $-4.0$ to 0.0; $P=0.459$), respectively. We found no significant difference between patients with and without FHP in terms of time-to-scan, with values of 97 versus 88 (IQR, 75–144.5 versus IQR 71.5–120; $P=0.67$).

**FHA**

Mortality rates did not differ significantly between patients with FHA and those without (8.3% versus 8.1%). Good functional outcome 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%; $P=0.03$), arterial occlusion (85% versus 21%; $P<0.01$), higher median NIHSS score (10 versus 5; IQR, 5–17 versus IQR, 4–8; $P<0.01$), higher median diffusion-weighted imaging lesion volume (5 mL versus 0.5 mL; IQR, 1.0–18.9 versus IQR, 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 IQR, 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 $-3$ (IQR, $-4$ to 0) versus $-2$ (IQR, $-5.0$ to 0.0; $P=0.658$), 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%, 25% 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...
mL (IQR, 0.0–4.7) versus 5.7 mL (IQR, 1.2–38.4; P = 0.045) in FRAP; median relative growth was 1.8 (IQR, 1.1–4.0) versus 2.2 (IQR, 1.5–3.1; P = 0.0742), and median change in NIHSS score was −3 (IQR, −4 to 0) versus −1 (IQR, −4.0 to 0; P = 0.770), respectively.

### 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 1 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 may be testimony for impaired hemodynamics and insufficient collaterals. Conflicting findings from previous studies may be partly attributable to differing methodologies. For instance, Schellinger 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.

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References
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