Can Diffusion-Weighted Imaging–Fluid-Attenuated Inversion Recovery Mismatch (Positive Diffusion-Weighted Imaging/Negative Fluid-Attenuated Inversion Recovery) at 3 Tesla Identify Patients With Stroke at <4.5 Hours?

Samuel Emeriau, PhD; Isabelle Serre, MD; Olivier Toubas, MD; Francis Pombourcq, MD; Catherine Oppenheim, MD, PhD; Laurent Pierot, MD, PhD

Background and Purpose—At 1.5 T, diffusion-weighted imaging–fluid-attenuated inversion recovery (DWI–FLAIR) mismatch helps identify strokes within 4.5 hours of onset. However, at 3T, studies have found divergent results. The goal of this study was to determine whether DWI–FLAIR mismatch at 3T would also be helpful for identifying patients within 4.5 hours of symptom onset.

Methods—All patients presenting with an ischemic stroke in the middle cerebral artery territory and explored with 3T MRI within 12 hours between November 2007 and April 2012 were included in this retrospective study. Two readers analyzed the DWI and FLAIR images. Logistic regression was performed to determine independent predictors of FLAIR visibility. Also, the predictive values of a mismatch for identifying patients with stroke onset ≤4.5 hours were estimated.

Results—The study included 194 patients. The only predictive factor of FLAIR visibility was delayed MRI acquisition. The DWI–FLAIR mismatch was able to identify patients within 4.5 hours of stroke onset with relatively low sensitivity (0.55; 95% confidence interval, 0.48–0.63), low specificity (0.60; 95% confidence interval, 0.42–0.77), high positive predictive value (0.88; 95% confidence interval, 0.82–0.94), and very low negative predictive value (0.19; 95% confidence interval, 0.11–0.28). In addition, 44.5% of patients had a positive FLAIR sequence within 4.5 hours.

Conclusions—This study improves our understanding of DWI–FLAIR mismatch as an imaging biomarker for wake-up management of patients with stroke. At 3T, the presence of a DWI–FLAIR mismatch was able to identify stroke onset of <4.5 hours. However, 44.5% of such stroke cases demonstrated FLAIR signal changes. (Stroke. 2013;44:1647-1651.)

Key Words: biomarker ■ brain imaging ■ ischemic stroke ■ MRI ■ penumbra stroke onset ■ thrombolysis acute stroke

Ischemic strokes are estimated to happen during sleep in 25% of cases, leading to an unknown time of symptom onset.1 International guidelines recommend intravenous thrombolysis within 4.5 hours of symptom onset, excluding patients with uncertain stroke times.2–4 Yet some authors have suggested there are no relevant differences in clinical (age, sex, stroke risk factors, stroke severity at admission, and vital signs) features and etiopathogenic stroke subtypes in patients with stroke on awakening and those with stroke while awake, suggesting that some patients with stroke on awakening may benefit from thrombolysis.5

Recently, some authors have suggested that the choice to treat a patient or not could be made on the basis of imaging parameters. It was proposed that a fluid-attenuated inversion recovery (FLAIR) sequence could estimate whether a stroke had taken place within the last 4.5 hours.6 Also, diffusion-weighted imaging (DWI) shows high signal intensity within the first minutes of stroke, allowing early diagnosis, whereas FLAIR signal changes are delayed. This increase in FLAIR signal has been used to discriminate between hyperacute (<4.5 hours after stroke onset) and acute ischemic strokes (>4.5 hours after stroke onset). Accordingly, the DWI–FLAIR mismatch (in other words, a positive DWI signal with a negative FLAIR signal) could be tested as a potential marker of strokes occurring within 4.5 hours. At 1.5 T, the DWI–FLAIR mismatch can be used to identify patients within 3 or 4.5 hours of symptom onset with high specificity and high positive predictive value (PPV).7,8 These results have been consistent between studies at 1.5T but not in the case of 3T. Some authors found no differences between the 2 field strengths, suggesting that the DWI–FLAIR mismatch could be used to detect patients with stroke of <4.5 hours irrespective of the magnetic field.9 Conversely, other authors do not recommend the use of FLAIR images to estimate time...
from symptom onset within the first 4.5 hours because of low sensitivity.10

The goal of the present study was to determine whether the DWI–FLAIR mismatch at 3T might be a good marker for identifying those patients who are within 4.5 hours of ischemic stroke symptom onset.

Materials and Methods

Patients

Patients with ischemic strokes in the middle cerebral artery territory who underwent 3T MRI at our institution during the first 12 hours of symptom onset were retrospectively studied during the period from November 2007 to April 2012. They were identified from the registry of the stroke unit. Patients were included if they had a precise time of stroke symptom onset and if they had undergone DWI and FLAIR imaging. The study had the approval of the local institutional review board. According to the study design, written informed consent was waived.

Initially, 234 patients were included in the study. Patients with FLAIR images showing major artifacts (n=20; 8.9%) were excluded, as were those with multiple lesions of different ages (n=20; 8.9%), because of the difficulty of attributing lesions to the stroke symptoms used to date it.11 Ultimately, data from 194 patients were analyzed.

For each patient, demographic data (sex, age), National Institutes of Health Stroke Scale (NIHSS) score at admission, and stroke symptom onset time to determine the stroke onset-to-MRI delay were collected.

MRI Protocol

The MRI study was performed on a 3T whole body clinical scanner (Achieva, Philips Medical Systems, Best, The Netherlands) with a 16-channel head coil. The protocol included the following 2 sequences: DWI sequence with a b value of 0 and 1000 s/mm², repetition time=2500 ms, echo time=55 ms, field of view=230×230 mm, matrix size=256×256, 28 slices, and slice thickness=5 mm without gap; and FLAIR sequence with repetition time=11 000 ms, echo time=125 ms, inversion time=2800 ms, field of view=230×230 mm, matrix size=512×512, 28 slices, and slice thickness=5 mm without gap.

Image Analysis

The imaging analysis was performed independently by 2 radiologists (O.T. and F.P.), who had >10 years of experience in reading stroke magnetic resonance images. They were given clinical information to better evaluate signals from the lesions corresponding to stroke symptoms and to ensure that stroke onset in relation to MRI delay was a good estimation of lesion age. They were also instructed to classify positive FLAIR results as either subtle or evident. The readers were also recommended not to take into account high intravascular signals corresponding to an early flow slowing down near the ischemic lesion.12 As done by others, patients with high signal intensity limited to the cortex in large stroke (half the vascular territory) were assigned to the negative FLAIR group. When the readers’ assessments differed, a consensus was reached. A third reader (S.E., with 3 years of experience) estimated the presence of leukoaraioisis on FLAIR images, according to the Fazekas scale, where 0, no white matter lesions; 1, multiple punctuate lesions; 2, early confluence of lesions; and 3, large confluent lesions.13 The same reader also estimated the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of lesions seen on diffusion-weighted images.14,15

Statistical Analysis

Age, sex, NIHSS at admission, Fazekas scale, ASPECTS, and stroke-to-MRI delay were compared between the negative FLAIR and positive FLAIR groups, using the χ² test for categorical variables or Student t test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed continuous variables. Interobserver agreement and Cohen κ coefficient were calculated for identification of the DWI–FLAIR mismatch. Logistic regression was used to identify independent predictors of mismatch. The evaluated factors were age, sex, NIHSS at admission, stroke onset-to-MRI delay, Fazekas scale, and ASPECTS. Also evaluated were the sensitivity, specificity, PPV, and negative predictive value of the FLAIR-negative images for identifying stroke of <4.5 hours. The impact of classifying cortical hyperintensities as FLAIR-negative images on predictive values was also evaluated.

The receiver operating characteristic curve was estimated to compare the function of negative and positive FLAIR images in the identification of stroke-to-MRI delay. The area under the curve and cutoff point to maximize sensitivity and specificity were also determined to find the delay that was best discriminated by the FLAIR imaging signal.

The statistical analyses used Epi Info (version 3.5.3) and Matrix Laboratory (version 7.10.0) software. P<0.05 was considered statistically significant.

<table>
<thead>
<tr>
<th>Negative FLAIR</th>
<th>No FLAIR signal change</th>
<th>Cortical FLAIR change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive FLAIR</td>
<td>Evident FLAIR signal change</td>
<td>Subtle FLAIR signal change</td>
</tr>
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</table>

Figure 1. The classification algorithm: for each example, diffusion-weighted imaging is on the left and fluid-attenuated inversion recovery (FLAIR) imaging is on the right.
Results

Patients

The study group comprised 194 patients aged 18 to 92 years (mean age, 65.0±13.7 years). There were 112 men aged 18 to 85 years (mean age, 63.2±13.4 years) and 82 women aged 34 to 92 years (mean age, 67.4±13.9 years). Of these patients, 164 were imaged at 0 to 4.5 hours after stroke onset and 30 were imaged in the 4.5- to 12-hour time window after stroke onset. Of the 164 patients imaged at 0 to 4.5 hours after stroke onset, 111 underwent IV thrombolysis as well as 4 out of 30 patients imaged at >4.5 h after stroke onset. In all cases, IV thrombolysis was administered after MRI completion. No patient had negative diffusion. According to the readers’ consensus, 121 of 194 patients (62.4%) had negative FLAIR and 73 of 194 (37.6%) had positive FLAIR results.

Agreement

Interobserver agreement in the detection of DWI–FLAIR mismatch was moderate, with an agreement of 79% and κ=0.58 (95% confidence interval [CI], 0.47–0.70). The divergences involved 40 patients. Among these cases, 1 reader found 25 patients who were FLAIR negative, while the other reader found 15 patients who were FLAIR negative.

Group Comparison

The 2 groups (FLAIR positive and FLAIR negative) were significantly different in terms of stroke-to-MRI delay, NIHSS at admission, and ASPECTS (Table 1). Logistic regression analysis confirmed this result (Table 2). In fact, only time between stroke onset and MRI was found to be an independent predictor of FLAIR signal hyperintensity. The odds ratio indicated that the probability of FLAIR being negative decreased by 11% for every 30-minute interval. Of the various predictors, age and Fazekas scale were correlated (r=0.45; P<0.001) but were not independent predictors.

Qualitative Analysis

Of the patients who had a stroke-to-MRI delay of <3 hours, 45 (43%) were FLAIR positive and 60 (57%) were FLAIR negative, whereas, of those with a delay between 3 and 4.5 hours, 28 (47%) were FLAIR positive and 31 (53%) were FLAIR negative. Furthermore, of those who had a delay of >4.5 hours, 18 (69%) were FLAIR positive and 8 (31%) were FLAIR negative (Figure 2). In the FLAIR-negative group, 91 patients (88%) had hyperacute stroke and 12 (12%) had acute stroke. In the FLAIR-positive group, 73 patients (80%) had hyperacute stroke and 18 (20%) had acute stroke. There were few false positives (12%) but many false negatives in our study (80%). DWI–FLAIR mismatch identified hyperacute patients with a sensitivity of 0.55 (95% CI, 0.47–0.63), a specificity of 0.60 (95% CI, 0.42–0.77), PPV of 0.88 (95% CI, 0.82–0.94), and negative predictive value of 0.19 (95% CI, 0.11–0.27). Ten patients presented with isolated cortical FLAIR hyperintensity. Their classification into the FLAIR-negative group had no significant impact on the predictive value of the DWI–FLAIR mismatch to identify patients with hyperacute stroke (Table 3).

In addition, the receiver operating characteristic analysis showed an area under the curve of 0.58 (95% CI, 0.50–0.66), indicating the quality of the prediction of the delay between symptom onset and imaging, according to the negativity of the FLAIR signal (Figure 3). The optimal cutoff time was 170 minutes.

Discussion

The term “DWI–FLAIR mismatch” was used to describe a lesion with a DWI hypersignal and an absence of FLAIR hypersignal, and is not consistent with the definition of mismatch when referring to perfusion-weighted imaging/DWI. Indeed, the FLAIR/DWI mismatch implies normal FLAIR findings, whereas the perfusion-weighted imaging/DWI mismatch refers to differences in the extent of perfusion-weighted imaging and DWI changes. It presents a relative ambiguity regarding the DWI–perfusion-weighted imaging mismatch, which refers to a difference in the size of the abnormality.

The main finding of the present study was that the DWI–FLAIR mismatch at 3T helped to identify patients whose strokes occurred within 4.5 hours with a high PPV. In other words, when the FLAIR signal was negative, in 88% of cases, the delay between MRI and stroke onset was <4.5 hours. This suggests that the 3T FLAIR sequence provides information that can be used to estimate the age of stroke.

It is, however, not sufficient for differentiating patients before and after 4.5 hours. Indeed, our results show moderate specificity, moderate sensitivity, and low negative predictive value. A large proportion of patients (44.5%) had a positive

### Table 1. Patient Demographics and Clinical and Imaging Scores in the FLAIR-Negative and FLAIR-Positive Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Negative FLAIR (n=121)</th>
<th>Positive FLAIR (n=73)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (median, IQR)</td>
<td>68 (58–75)</td>
<td>66 (51–76)</td>
<td>0.231</td>
</tr>
<tr>
<td>Sex, male (n, %)</td>
<td>59 (57)</td>
<td>53 (58)</td>
<td>0.504</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>13 (7–19)</td>
<td>10 (5–16)</td>
<td>0.022</td>
</tr>
<tr>
<td>Fazekas scale, mean (SD)</td>
<td>1.11 (0.0–2)</td>
<td>0.9 (0–1.8)</td>
<td>0.321</td>
</tr>
<tr>
<td>ASPECTS, mean (SD)</td>
<td>7.5 (6.0–9.0)</td>
<td>7.9 (6.6–9.2)</td>
<td>0.028</td>
</tr>
<tr>
<td>Time to MRI, median (IQR)</td>
<td>167 (125–210)</td>
<td>180 (160–230)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

*ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

*Mann–Whitney U test.

### Table 2. Multivariate Analysis

<table>
<thead>
<tr>
<th>Group Characteristics</th>
<th>Estimated Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 years)</td>
<td>1.06 (0.94–1.21)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.92 (0.49–1.71)</td>
</tr>
<tr>
<td>NIHSS at admission</td>
<td>1.02 (0.97–1.07)</td>
</tr>
<tr>
<td>Fazekas scale</td>
<td>1.10 (0.79–1.54)</td>
</tr>
<tr>
<td>ASPECTS</td>
<td>0.87 (0.67–1.14)</td>
</tr>
<tr>
<td>Time to MRI (per 30 min)</td>
<td>0.89 (0.80–0.98)</td>
</tr>
</tbody>
</table>

Logistic regression was used to estimate negativity of the fluid-attenuated inversion recovery signal. ASPECTS indicates Alberta stroke program early computer tomography score; CI, confidence interval; and NIHSS, National Institutes of Health Stroke Scale.
FLAIR within 4.5 hours, which means that 44.5% of strokes of <4.5 hours’ onset were not identified by the DWI–FLAIR mismatch. Further preferably prospective studies have to be conducted at 3T to confirm this high percentage of patients with hyperacute stroke and FLAIR positivity. We found higher sensitivity, but lower specificity than other groups who analyzed 3T FLAIR images.10 These differences can be explained by the fact that our study excluded multiple lesions of different ages, and our readers were not blinded to the clinical symptoms of stroke. This might have minimized false positives and increased sensitivity and PPV.10 Another explanation could have been differences in FLAIR sequence parameters or in the number of channels on the head coil, which can significantly affect the FLAIR signal. In addition, the specificity we found was lower than that found at 1.5T, which may be explained by the greater visibility of FLAIR lesions at 3T. Finally, when symptom onset is not precisely known (wake-up stroke), FLAIR negativity indicates with a high PPV that the delay between stroke onset and MRI is <4.5 hours. Conversely, FLAIR positivity can be encountered in patients with hyperacute stroke, an important limitation (eligible patients for IV tissue-type plasminogen activator can be missed FLAIR only is considered).

Multiparametric analysis of our present data could find no independent predictors of FLAIR visibility except for the stroke-to-MRI delay. Patient age, leukoaraiosis (which was significantly correlated with age), NIHSS at admission, sex, and ASPECTS were not predictive of DWI–FLAIR mismatch. Although age, leukoaraiosis, and DWI lesion volume are often confounding factors of FLAIR visibility, these factors had no such impact on our results.7,10 No significant differences were highlighted, not even when the ASPECT score was considered representative of lesion volume.15

Our classification, made by visual evaluation of FLAIR signals, led to fair interobserver agreement, despite exclusion of early intra-arterial hyperintense FLAIR signals and the cortical part of large strokes from the FLAIR-positive group. Similar results were observed in previous 3T studies.9,10 Classifying isolated cortical FLAIR hypersignals has no major impact on sensitivity or specificity (Table 3). On the contrary, the sometimes difficult depiction of subtle changes on FLAIR images can affect interobserver agreement. Because the readers were not requested to distinguish between evident and subtle FLAIR changes, this parameter cannot be analyzed in our series. To overcome the problem of subtle changes on FLAIR images, quantitative analysis of the relative signal of the lesion compared with the contralateral side is potentially helpful. At 1.5T, it has been demonstrated that a value of 7% of the FLAIR signal ratio (between stroke and contralateral parenchyma) may be the best cutoff point for discriminating hyperacute from acute strokes.7 Similar research needs to be done to evaluate the ratio value at 3T, which will most likely be higher than at 1.5T. The major drawback of this kind of methodology is its limited usefulness in routine clinical work.

In our study, the time between symptom onset and MRI acquisition was evaluated as a potential predictor of the FLAIR signal. The link between FLAIR signal intensity and time is not yet fully understood, but our findings have demonstrated that the cutoff delay between symptom onset and MRI that best predicts FLAIR positivity was 170 minutes, which is less than the thrombolysis delay. This highlights the precocity of FLAIR signal positivity at 3T and explains the difference in results in comparison with 1.5T.

Our study has several limitations. The first is the small number of patients in the 4.5- to 12-hour time window.

### Table 3. Predictive Values of FLAIR Negativity for Identifying Patients With Delay Between Stroke Onset and MRI Within 4.5 Hours While Considering Cortical FLAIR Hyperintensity as FLAIR Negative or FLAIR Positive

<table>
<thead>
<tr>
<th>Cortical FLAIR Hyperintensity Group</th>
<th>Se (95% CI)</th>
<th>Sp (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative FLAIR</td>
<td>0.55 (0.47–0.63)</td>
<td>0.60 (0.42–0.77)</td>
<td>0.88 (0.82–0.94)</td>
<td>0.19 (0.11–0.27)</td>
</tr>
<tr>
<td>Positive FLAIR</td>
<td>0.52 (0.44–0.59)</td>
<td>0.63 (0.46–0.80)</td>
<td>0.88 (0.82–0.95)</td>
<td>0.19 (0.11–0.27)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; FLAIR, fluid-attenuated inversion recovery; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; and Sp, specificity.
positive, the delay between stroke onset and imaging is rather
patients with stroke-to-MRI delays <4.5 hours. If FLAIR is
DWI–FLAIR mismatch (FLAIR negative) can help to identify
in wake-up management of patients with stroke. At 3T, the
ing of DWI–FLAIR mismatch as an imaging biomarker
studies have found no differences in FLAIR–DWI mismatch,
mismatch. Finally, stroke subtypes were not studied, but other
studies may precisely identify the true value of DWI–FLAIR
the retrospective nature of our analysis. Further prospective
value of the DWI–FLAIR mismatch. Another limitation is
vertebrobasilar stroke and lacunar infarcts may determine the
results cannot be extrapolated to the anterior cerebral artery
4.5 and 5 hours after stroke onset, which might explain the
smaller difference in median delay time between our 2 groups
Furthermore, half of these patients were imaged between 4.5 and 5 hours after stroke onset, which might explain the
smallest difference in median delay time between our 2 groups
than seen in other studies. Nevertheless, the difference in the
number of patients included in the hyperacute versus acute stroke
groups can be explained by the fact that, in our institution,
patients with stroke onset >4.5 hours more often undergo
computed tomography or 1.5T MRI. A second limitation is
that we focused on middle cerebral artery stroke, and our
results cannot be extrapolated to the anterior cerebral artery
and vertebrobasilar territories. Further studies on patients with
vertebrobasilar stroke and lacunar infarcts may determine the
value of the DWI–FLAIR mismatch. Another limitation is the
retrospective nature of our analysis. Further prospective
studies may precisely identify the true value of DWI–FLAIR
mismatch. Finally, stroke subtypes were not studied, but other
studies have found no differences in FLAIR–DWI mismatch,
according to etiologic stroke subtypes.³

In summary, our present study improves the understanding
of DWI–FLAIR mismatch as an imaging biomarker in wake-up management of patients with stroke. At 3T, the
DWI–FLAIR mismatch (FLAIR negative) can help to identify patients with stroke-to-MRI delays <4.5 hours. If FLAIR is
positive, the delay between stroke onset and imaging is rather
variable and possibly <4.5 or >4.5 hours and then cannot be
used to make therapeutic decisions. However, it may be of
value in evaluating multiparametric MRI based on quantitative
data, including FLAIR signals, to determine whether identifi-
cation of hyperacute and acute strokes can be improved.

Disclosures
None.

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