Validity of Negative High-Resolution Diffusion-Weighted Imaging in Transient Acute Cerebrovascular Events

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Background and Purpose—A significant amount of strokes are reported to be diffusion-weighted imaging (DWI) negative in acute imaging. We attempted to quantify the rate of false-negative high-resolution (hr) DWI and to identify a valid screening tool to guide follow-up MRI to diagnose infarction initially not visible on hrDWI.

Methods—An a priori–defined post hoc analysis of a prospective 3T MRI cohort of acute cerebrovascular events imaged within 24 hours of ictus. Basic demographics, risk factors, National Institute of Health Stroke Scale, and imaging parameters were recorded.

Results—Of 151 patients with negative acute hrDWI, 63 received follow-up scans depicting infarction in 7 cases (11.1%). Persistence of clinical symptoms as established by National Institute of Health Stroke Scale on the following day was strongly associated with infarction on follow-up MRI (odds ratios, 17.5; 95% confidence interval, 2.83–108.12). Negative predictive value of follow-up National Institute of Health Stroke Scale was 0.96.

Conclusions—Infarcts are frequently invisible on initial hrDWI, but we may well trust in negative hrDWI in completely transient cerebrovascular events. (Stroke. 2013;44:00-00.)

Key Words: diffusion-weighted MRI ■ infarction ■ transient ischemic attack

The classical definition of transient ischemic attacks (TIAs) as focal neurological deficits resulting from ischemia lasting <24 hours has recently been challenged. Advances in neuroimaging lead to a tissue-based definition of focal neurological deficits without imaging proof of tissue infarction.1 Diffusion-weighted MRI (DWI) allows for an early sensitive diagnosis of ischemic injury and is the clinical gold standard to distinguish stroke and TIA, with a positive and negative predictive value of 98.5% and 69.5%, respectively.2,3 Increased resolution was shown to lower false-negative DWI rates significantly, thus Benameur et al4 coined the term high-resolution DWI (hrDWI). Significant amounts of DWI-negative strokes have been reported, of which ≤23.1% show DWI lesions on follow-up.5 This may lead to doubt about the imaging finding’s reliability in a clinical setting suggestive for a TIA or stroke. Especially lacunar stroke and infratentorial location seem to be negative predictors of DWI proof of infarction.1,6 No screening tool is currently available to guide scarce resources toward patients who should receive a follow-up scan to detect initially invisible infarction. We investigated whether acutely hrDWI-negative patients would prove to show infarction in follow-up examinations to a significant extent, and if so, whether there was an association with duration of symptoms. We hypothesized that acute hrDWI would be sufficiently reliable in patients with transient symptoms and that a follow-up examination is recommended in patients with a syndrome persisting for ≥24 hours.

Methods

Patient Selection

Data are derived from a prospective cohort study as a priori–defined sub-project of the 1000Plus study (http://clinicaltrials.gov NCT00715533) and received approval by the local ethics committee. Full methodology of 1000Plus has previously been reported.7 All patients gave informed consent. Inclusion criteria for this substudy were negative DWI on admission, MRI performed within 24 hours of ictus, and age ≥18 years.

Stroke MRI

Imaging studies were conducted using a 3T MRI system (Siemens Trio Tim 3T, Erlangen, Germany). hrDWI parameters were as follows: TR 7600 ms, TE 93 ms, 2 averages, FOV 230 mm, matrix 192×192, 50 gapless slices of 2.5 mm thickness, acquisition time 131 s, with a 6-direction diffusion tensor imaging. Apparent diffusion coefficient values were obtained and used to verify cytotoxic edema. Additional sequence parameters have been provided elsewhere.7 We included dichotomized (≤12 versus >12 hours) event to imaging delay in our analysis to correct for a possible bias from hyperacute imaging. Patient MRI scans were also rated for extent of leukaraiosis using the age-related white matter changes score.8 A high load of white matter changes might lead to shine through on DWI and render diagnosis difficult. For analysis, age-related white matter changes was dichotomized into low and high (≥4) lesion load.
Clinical Evaluations

All patients underwent neurological workup and were screened for cerebrovascular risk factors. National Institute of Health Stroke Scale (NIHSS) scores were rated at admission and follow-up. NIHSS scores were dichotomized into lack (NIHSS=0) and presence of symptoms (NIHSS≥1) for analysis.

Statistical Analysis

All analyses were performed using SPSS version 20 (IBM, Armonk, NY). Categorical variables were compared using Fisher exact test. Odds ratios (ORs) were calculated where appropriate to determine strength of association. Negative predictive value for dichotomized NIHSS was calculated to affirm validity as screening tool. Because of sample size, Bonferroni adjustments were chosen instead of multivariate analysis.

Results

One hundred and fifty-one patients with suspected acute cerebrovascular event and normal acute hrDWI were included in the analysis. Cerebrovascular risk factors and clinical evaluations are presented in Table 1. The mean age was 62.1 years and 51% of the cohort were female subjects. The mean time from symptom onset to acute MRI was 659 (SD±412) minutes. Sixty-three subjects received follow-up MRI scans, 7 of whom had a positive DWI on the following day (11.1%). Median NIHSS on the following day after symptom onset for DWI-positive patients was 2 (interquartile range, 0–4) and for DWI-negative patients was 0 (interquartile range, 0–0).

NIHSS on the day after symptom onset had an OR of 17.5 (95% confidence interval, 2.83–108.12) for diffusion restriction on follow-up imaging (Table 2). Atrial fibrillation (OR, 5.15; 95% confidence interval, 0.95–27.98) was borderline associated with follow-up DWI restriction. However, only NIHSS on the day after admission remained significant after Bonferroni adjustment for multiple testing. Negative predictive value, specificity, and sensitivity for follow-up dichotomized NIHSS for infarction observed by DWI was 0.96, 0.88, and 0.71, respectively.

Discussion

Negative acute DWI may lead to diagnostic uncertainty because of doubt concerning its validity. Seven patients showed DWI abnormalities on follow-up imaging, resulting in a substantial false-negative rate of 11.1% for baseline hrDWI (Figure). Of those patients who had a negative DWI on the second day (n=56), only 7 (12.5%) had an NIHSS of >0. Of those patients who did show DWI abnormalities on the second day (n=7), a total of 5 (71.4%) had an NIHSS of >0. Using NIHSS to triage for follow-up MRI would have led to a false-negative rate of 3.2%, with an overall reduction of examinations of 81.0%. This is further expressed by a negative predictive value of 0.96.

Our analysis showed that the NIHSS on the second day was significantly associated with diffusion restriction in follow-up exams with a strong OR of 17.5. A similar association was seen by other authors, who found a strong association of prolonged symptom duration with DWI positivity in patients with an acute ischemic event.9,10 The previous studies did not use hrDWI, leading to a lower sensitivity for ischemic lesions.4 Furthermore, no patients in our cohort showed lesions on the initial scan, representing the newly defined imaging- or tissue-based TIAs.

Table 2. Association Between Clinical Evaluations and Cerebrovascular Risk Factors to DWI Restriction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS &gt;0 on day 2</td>
<td>17.5 (2.83–108.12)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age</td>
<td>…</td>
<td>0.826</td>
</tr>
<tr>
<td>Sex</td>
<td>1.91 (0.39–9.37)</td>
<td>0.449</td>
</tr>
<tr>
<td>NIHSS score at admission</td>
<td>…</td>
<td>0.005</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>…</td>
<td>0.585</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.09 (0.19–6.25)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyperlipoproteinemia</td>
<td>0.70 (0.14–3.41)</td>
<td>0.708</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5.14 (0.95–27.98)</td>
<td>0.076</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.30 (0.03–2.67)</td>
<td>0.408</td>
</tr>
<tr>
<td>Known hypertension</td>
<td>0.64 (0.13–3.16)</td>
<td>0.698</td>
</tr>
<tr>
<td>Imaging delay (dichotomized)</td>
<td>0.17 (0.02–1.55)</td>
<td>0.191</td>
</tr>
<tr>
<td>Perfusion deficit</td>
<td>1.22 (0.20–7.33)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

ARWMC indicates age-related white matter changes; FU, follow-up; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; and TIA, transient ischemic attack.
This study was underpowered to exclude atrial fibrillation safely as a confounding factor, especially because it showed a trend of association with the outcome (OR, 5.14; 95% confidence interval, 0.95–27.98). However, studies have shown that TIA patients with underlying cardiac abnormalities are more likely to show infarction on acute DWI.11 We cannot distinguish whether infarctions seen on follow-up hrDWI were the cause of initial symptoms or new infarctions unrelated to the initial event. Furthermore, only 41.7% of the subjects agreed to follow-up scans; therefore, selection bias cannot be safely ruled out. A higher follow-up rate would allow for higher statistical power.

In conclusion, these data provide us with evidence that infarcts in patients with minor deficits are rather frequently invisible on initial hrDWI, and we may well trust in negative hrDWI for transient cerebrovascular events.

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Disclosures
None.

References
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