Negative Diffusion-Weighted Imaging After Intravenous Tissue-Type Plasminogen Activator Is Rare and Unlikely to Indicate Averted Infarction

Jason W. Freeman, MD; Marie Luby, PhD; José G. Merino, MD; Lawrence L. Latour, PhD; Sungyoung Auh, PhD; Shlee S. Song, MD; Alejandro Magadán, MD; John K. Lynch, DO; Steven Warach MD, PhD; Amie W. Hsia, MD

Background and Purpose—Some patients treated with intravenous (IV) tissue-type plasminogen activator (tPA) have negative diffusion-weighted imaging (DWI) on follow-up imaging. Without a visible infarct, there may be uncertainty as to whether the patient was having a stroke that was averted by tPA or whether the symptoms had not been cerebrovascular in origin. We evaluated patients presenting with suspected acute stroke with a positive DWI lesion before IV tPA to determine the probability of finding a negative DWI up to 48 hours after treatment.

Methods—We included patients from the Lesion Evolution in Stroke and Ischemia On Neuroimaging (LESION) project who had acute MRI screening with a positive DWI lesion before IV tPA treatment and had follow-up MRI up to 48 hours later. Experienced readers interpreted all acute and follow-up MRIs looking for ischemic lesions on DWI.

Results—There were 231 patients who met study inclusion criteria, of which 225 patients (97.4%) had a persistent positive DWI corresponding to the acute stroke lesion on all follow-up imaging. Four patients (1.7%) had transient DWI lesion reversal with positive DWI on subsequent follow-up imaging. There were only 2 cases (0.9%) of complete DWI lesion reversal on all follow-up imaging.

Conclusions—Averted infarction after IV tPA is rare, occurring in 0.9% of patients with pretreatment positive DWI evidence of acute ischemia. For IV tPA-treated patients who have a negative DWI on follow-up imaging, a cause other than acute stroke should be explored. (Stroke. 2013;44:00-00.)

Key Words: acute stroke ■ diffusion-weighted imaging ■ MRI ■ tPA ■ thrombolytic therapy

Most patients treated with intravenous tissue-type plasminogen activator (IV tPA) are screened with a head computed tomography before treatment. A head computed tomography excludes the presence of hemorrhage but does not confirm the presence of acute ischemia. In an unknown percentage of patients, the follow-up MRI may also fail to reveal a stroke. It is often difficult to conclude whether these patients had a stroke that completely resolved, a neuroimaging-negative stroke, or a stroke mimic. Several authors report that up to 17% to 26% of patients treated with IV tPA lack evidence of acute infarction on follow-up imaging, and 7% to 11% are classified as resolved or averted stroke.¹⁻⁵ The purpose of our study was to determine the incidence of averted infarction (defined as a clinically relevant baseline stroke syndrome in patients with positive pretreatment diffusion-weighted imaging [DWI], negative post-treatment DWI, and negative fluid attenuated inversion recovery within 48 hours of treatment) in a large stroke cohort.

Patients

This study includes patients evaluated by the National Institutes of Health Stroke Team for possible stroke at 2 hospitals—Suburban Hospital and Medstar Washington Hospital Center. Both the hospitals are primary stroke centers certified by The Joint Commission. The same group of board-certified vascular neurology attending physicians and fellows staff the National Institutes of Health Stroke Team at both the hospitals and serve as the designated acute stroke response teams. Between August 1999 and October 31, 2009, the National Institutes of Health Stroke Team at both hospitals had a total of 3985 patients with an admission diagnosis of acute ischemic stroke or transient ischemic attack. The stroke team prospectively recorded clinical and demographic data of the 3985 patients, there were 1167 patients who were either (1) screened with MRI within 24 hours of witnessed stroke onset with an admission diagnosis of ischemic stroke or transient ischemic attack. The stroke team prospectively recorded clinical and demographic data of the 3985 patients, there were 1167 patients who were either (1) screened with MRI within 24 hours of witnessed stroke onset with an admission diagnosis of acute ischemic stroke or transient ischemic attack and National Institutes of Health Stroke Scale >3 on admission or (2) had a pretreatment MRI and received an acute intervention. These 1167 patients were included...
in the Lesion Evolution in Stroke and Ischemia On Neuroimaging (LESION) project.

Patients from the LESION project were included in this study if they had a pretreatment MRI with a positive DWI lesion, were treated with standard IV tPA at either hospital, and had at least 1 follow-up MRI within 48 hours of tPA treatment. Patients treated with standard IV tPA were excluded from this study if they had a pretreatment MRI with a negative DWI lesion with or without a positive perfusion-weighted imaging (PWI) lesion. Office of Human Subjects Research exemptions and local institutional review board approvals (National Institute of Neurological Disorders and Stroke, Suburban, and Medstar Health Research Institute) were obtained for use of clinical and research data.

**Imaging Protocol**

Imaging was performed using clinical MRI scanners, 1.5T (Twinspeed, General Electric) at Suburban Hospital or a 3.0T (Achieva, Philips) at Medstar Washington Hospital Center. The pretreatment MRI protocol at each clinical site included DWI, PWI, fluid attenuated inversion recovery, gradient-recalled echo, and MR angiography. The MRI protocol was typically repeated at 2 hours after tPA, as well as at 24 hours and 3 to 5 days or before discharge. DWI and PWI series were acquired colocalized over the entire brain with a superior to inferior coverage of 14 cm. Typical imaging parameters for DWI spin-echo echo-planar series included either 40- to 3.5-mm or 20- to 7-mm-thick contiguous axial oblique slices with $b=0$ and $b=1000 \text{ s/mm}^2$, trace or isotropically weighted, repetition time/echo time=6000 to 7000/72 to 90 ms, acquisition matrix of 64×64 to 128×128, and 22-cm field of view. The PWI was a dynamic susceptibility contrast series using a single dose of 0.1 mmol/kg of gadolinium. Typical imaging parameters for PWI gradient-echo planar series included 20 contiguous axial oblique slices with single-dose gadolinium contrast injection of 0.1 mmol/kg through a power injector using 25 to 40 phase measurements, repetition time/echo time=2000 to 2200/45 ms, acquisition matrix of 64x64 to 128x128, 7-mm slice thickness, and 22-cm field of view.

**Imaging Analysis**

Readers (M.L., J.G.M., L.L.L., S.S.S., J.K.L., A.M., S.W., A.W.H.) experienced in stroke MRI interpretation reviewed the baseline MRI to identify areas of ischemia on DWI, perfusion deficit on mean transit time maps, and extracranial carotid or intracranial carotid or M1 segment occlusion or abnormal M1, M2, anterior cerebral artery, basilar or posterior cerebral artery segments. After performing any study reads, each of the 7 readers independently evaluated the same set of 10 training cases for qualification purposes. The results of these training cases were compared with the consensus reviews of these same cases performed during neuroimaging rounds. A reader was qualified if >90% of their interpretations, that is, 9 of 10 cases, were consistent with the consensus reviews for DWI, PWI, and MR angiography. There was no adjudication of the study reads. For these reads, a Digital Imaging and Communications in Medicine image viewer was used by the independent reader or by the consensus group of readers to visualize the entire acute MRI study to determine the presence of ischemia, perfusion deficit, and site of occlusion, as well as any other stroke pathologies relevant to the study.

**Table. Patient Characteristics According to Diffusion-Weighted Imaging Lesion Pattern**

<table>
<thead>
<tr>
<th></th>
<th>Persistent DWI Lesion Stroke (n=225)</th>
<th>Transient DWI Lesion Reversal Stroke (n=4)</th>
<th>Averted Infarction (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (±SD)</td>
<td>71.6 (±15.2)</td>
<td>62.3 (±25.5)</td>
<td>44.5 (±6.4)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>122 (54%)</td>
<td>2 (50%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>159 (71%)</td>
<td>4 (100%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>57 (25%)</td>
<td>0</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>9 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic origin, n (% yes)</td>
<td>7 (3%)</td>
<td>1 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Median admit NIHSS (IQR, 25–75)</td>
<td>10 (5–18)</td>
<td>2 (1–9)</td>
<td>5 (3–5)*</td>
</tr>
<tr>
<td>Median acute DWI lesion volume, mL (IQR, 25–75)</td>
<td>12.1 (2.5–50.4)</td>
<td>4.1 (1.8–10.6)</td>
<td>1.29 (0.16–1.29)*</td>
</tr>
<tr>
<td>Acute PWI lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>178 (78%)</td>
<td>4 (100%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>No, n (%)</td>
<td>17 (8%)</td>
<td>0</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Hypertension, n (% yes)</td>
<td>160 (71%)</td>
<td>2 (50%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (% yes)</td>
<td>114 (51%)</td>
<td>1 (25%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Atrial fibrillation or atrial flutter, n (% yes)</td>
<td>71 (32%)</td>
<td>1 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus, n (% yes)</td>
<td>48 (21%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CAD/CABG/PTCA, n (% yes)</td>
<td>62 (28%)</td>
<td>0</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>CAD, n (% yes)</td>
<td>22 (10%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Previous ischemic stroke or TIA, n (% yes)</td>
<td>52 (23%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median discharge mRS (IQR, 25–75)</td>
<td>3 (1–5)</td>
<td>0 (0–2)</td>
<td>1 (0–1)*</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; DWI, diffusion-weighted imaging; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PTCA, percutaneous transluminal coronary angioplasty; PWI, perfusion-weighted imaging; and TIA transient ischemic attack.

*(IQR, 25–50).*
to the acute index lesion. The readers were not blinded to the date and time of the MRI study and were able to compare the current study with any prior MRI studies acquired for the study patient. The readers were unaware of the planimetric quantitative DWI volume results. On the basis of the imaging findings of these patients who all had positive pretreatment DWI lesions, patients were categorized as persistent DWI lesion stroke (positive post-treatment DWI), transient DWI lesion reversal (early negative post-treatment DWI with a subsequent follow-up scan again showing the index DWI lesion), or averted infarction (negative post-treatment DWI and fluid attenuated inversion recovery within 48 hours).

A rater (M.L.) with extensive experience and established rater reliability statistics measured the lesion volumes on the DWI and MTT maps using a semiautomated quantitative, planimetric method in Cheshire. Additional raters (J.G.M., S.W.) are qualified to perform these planimetric measurements. The intra- and inter-rater reliability of the planimetric measurements of DWI and MTT has been validated as a highly consistent and repeatable method using Cheshire. However, to minimize measurement variability for the acute intervention patients, 1 rater (M.L.) performed the quantitative measurements well in advance to the prospective identification of the patients eligible for the LESION project. Lesion areas were segmented on a slice-by-slice basis with user-selected seed points followed by user-driven editing. DWI lesions were identified on affected hyperintense areas visible from the $b=1000 \text{ mmol/s}^2$ trace or isotropic images. The rater was careful not to include bilateral artifacts, chronic lesions and if necessary, reviewed apparent diffusion coefficient maps to isolate acute lesions. The volumes were automatically calculated by multiplying the total lesion area by the slice thickness.

**Statistical Analysis**

The patient characteristics were grouped according to DWI lesion pattern and the variables were summarized using mean ($\pm$SD) and median (interquartile range, 25–75) as appropriate (Table). Percentages of risk factors for each group were also calculated. Given the small number of patients in the averted infarction and transient DWI lesion reversal stroke groups, only descriptive comparisons were included.

**Results**

The LESION project included 267 patients who had a pretreatment MRI performed before IV tPA. Of these, 231 met study inclusion criteria. The median time (interquartile range, 25–75) from stroke onset, defined as time last known well, to IV tPA bolus was 159 (131–178) minutes. The median time from start of pretreatment MRI to IV tPA bolus was 46 (35–62) minutes. The median time from IV tPA bolus to 2-hour MRI was 109 (88–138) minutes and to 24-hour MRI was 23.9 (22.6–25) hours.

The patients are grouped according to their DWI lesion pattern (Table). Of the 231 patients, 225 (97.4%) had a persistent DWI lesion on all follow-up MRIs up to 48 hours after treatment. The median baseline DWI lesion volume was 12.1 mL (interquartile range, 25–75; 2.5–50.4 mL). The median baseline National Institutes of Health Stroke Scale was 10 (interquartile range, 25–75; 5–18). In addition, 4 patients (1.7%) had transient DWI lesion reversal on the 2-hour follow-up scan with reappearance of the DWI lesion at 24 hours. For the 4 transient DWI lesion patients, the median baseline DWI lesion volume was 4.1 mL (1.8–10.6 mL). The median baseline National Institutes of Health Stroke Scale was 2 (1–9). Three of these 4 patients had infarcts in the frontal lobe and 1 in the cerebellum. An example of a patient with a transient reversal is displayed in Figure 1.

**Figure 1.** Example of transient diffusion-weighted imaging (DWI) lesion reversal. An 81-year-old woman with acute onset left hemiparesis and dysarthria, National Institutes of Health Stroke Scale of 1, with a transient DWI lesion reversal pattern: positive DWI lesion (A) on pretreatment MRI, negative DWI (B) and apparent diffusion coefficient (not shown) at 2 h after treatment with intravenous tissue-type plasminogen activator but positive DWI at 24 h (C) and positive fluid attenuated inversion recovery (D) at 5 days.
Only 2 patients (0.9%) had an averted infarction. These patients had a positive DWI lesion on the pretreatment MRI and did not have a corresponding abnormality on any follow-up MRI including DWI and fluid attenuated inversion recovery. The clinical and imaging characteristics of these patients with averted infarction are presented in Figures 2 and 3. One patient had a punctuate (0.16 mL) DWI lesion in the medulla consistent with the clinical syndrome; the presumed pathogenesis was a vertebral artery dissection (Figure 2). The other patient had a small (2.41 mL) index lesion on DWI in the left frontal lobe and additional satellite lesions in multiple vascular territories (Figure 3). Both the patients had complete resolution of their clinical symptoms at discharge. These patients were younger with smaller baseline DWI lesion volumes than those with persistent DWI lesions or transient DWI lesion reversal (Table).

The averted infarction and transient DWI lesion reversal patients had lower baseline National Institutes of Health Stroke Scale scores compared with the persistent DWI lesion patients (Table).

**Discussion**

We found that complete DWI lesion reversal (averted infarction) is extremely rare after treatment with IV tPA: <1% of patients with a DWI lesion before treatment had a negative DWI after IV tPA. To our knowledge, this is the first study of averted infarction in patients with an MRI before and after treatment.

Earlier studies have reported a higher rate of negative MRI after IV tPA. However, in these studies of patients with a clinical stroke syndrome, computed tomography was the primary pretreatment imaging modality and an MRI was only obtained after treatment. In a series of 254 patients, Uchino et al.\(^1\) found that 8.3% had a radiographic transient ischemic attack with full recovery of symptoms and negative DWI and 3.5% had a stroke mimic. Chang et al.\(^4\) found that 11% of patients had an aborted stroke (those with sudden focal neurological dysfunction without MRI signs of acute ischemia that received a final clinical diagnosis of acute ischemic stroke) and 15% had a stroke mimic (those without neuroimaging findings whose final diagnosis was not acute ischemic stroke). Chernyshev et al.\(^2\) reported that 7% of their IV tPA-treated patients had neuroimaging-negative cerebral ischemia, which they equate to averted stroke, and 14% had a stroke mimic. These studies did not consistently have pretreatment MRI, and it is possible that the higher rates of MRI-negative stroke after tPA are because of initial reliance on clinical judgment.

In a recently published study that did require consistent pre- and post-treatment MRI evaluating the extent of any acute DWI lesion reversal after thrombolysis, Labeyrie et al.\(^7\)
found that 50% of patients had some DWI lesion reversal involving >11% of the initial DWI lesion volume. However, only 4% (7 of 176) had total or subtotal (>95%) DWI reversal 24 hours after treatment. This study did not distinguish transient versus persistent reversal.

We observed transient reversal of the entire DWI index lesion in 4 patients (1.7%) who had a repeat MRI 112 minutes after tPA initiation; in all instances, the DWI lesion was again seen at 24 hours. Other studies have reported this phenomenon in both animal models and in humans after reperfusion. These findings underscore the need for repeat imaging in patients with a negative DWI but high suspicion of stroke. However, by 24 hours, >99% of patients in our cohort were DWI positive.

Limitations of this study include the 10-year span of the study time period. MRI quality has improved significantly during this time with increasing sensitivity of MRI for visualizing early and small infarcts. Because our averted stroke patients had smaller lesion volumes compared with our persistent DWI lesion strokes, one may question whether these smaller lesions were simply missed on follow-up MRI limited by image quality. However, our averted stroke patients were treated more recently in 2007 and 2009 with higher quality imaging that were determined to be evaluable by experienced readers; therefore, the disappearance of the index lesions is not likely because of poor image quality. Similarly, the transient DWI lesion reversal seen in 4 patients, treated between 2002 and 2007, was not related to image quality. Finally, we did not characterize collateral protection for these patients which may affect DWI lesion reversal. This is an area for future study.

Conclusions

Patients with a stroke are unlikely to have complete DWI lesion reversal within 24 hours after IV tPA treatment. When follow-up MRI is negative, particularly in patients whose stroke is not suspected to be in the brain stem, it is important to consider pathogeneses other than acute stroke to avoid missing other treatable conditions or subject a patient to the implications associated with incorrectly carrying a diagnosis of stroke or transient ischemic attack.

Acknowledgments

We acknowledge and thank the National Institutes of Health Stroke Team, the staffs of Suburban Hospital (Bethesda, MD) and Medstar Washington Hospital Center (Washington, DC), and the patients for their valuable participation and cooperation.
Sources of Funding
This research was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Neurological Disorders and Stroke.

Disclosures
Merino receives salary support from Biomedical Journal for his role as US clinical research editor. The other authors have no conflicts to report.

References
Negative Diffusion-Weighted Imaging After Intravenous Tissue-Type Plasminogen Activator Is Rare and Unlikely to Indicate Averted Infarction

Jason W. Freeman, Marie Luby, José G. Merino, Lawrence L. Latour, Sungyoung Auh, Shlee S. Song, Alejandro Magadán, John K. Lynch, Steven Warach and Amie W. Hsia

Stroke. published online April 9, 2013;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 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/early/2013/04/09/STROKEAHA.111.000486

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/