Diffusion-Weighted Magnetic Resonance Imaging Identifies the “Clinically Relevant” Small-Penetrator Infarcts

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Background: Most patients initially seen with a clinical syndrome consistent with a small-penetrator infarct (SPI) also harbor multiple, chronic, hyperintense, white matter lesions on conventional magnetic resonance imaging (ie, T2-weighted image [T2WI] and fluid-attenuation inversion recovery [FLAIR] imaging). Diffusion-weighted imaging (DWI) can identify the clinically relevant “index infarction” in such circumstances, since it differentiates between acute and chronic lesions.

Objective: To determine the clinical and radiological predictors associated with misidentification of an SPI as acute using T2WI and FLAIR images in patients with an acute SPI seen on DWI.

Patients: Sixty-seven consecutive patients who had an SPI.

Methods: Two independent examiners, provided with brief clinical information, but blinded to DWI findings, sought a clinically appropriate lesion on T2WI and FLAIR imaging in 67 consecutive patients found to have an SPI seen on DWI.

Results: The index infarction based on evaluation of T2WI or FLAIR images was in a different location than the acute lesion as identified by DWI in 9 (13%) and 11 (16%) of 67 patients, respectively. Both T2WI and FLAIR imaging were rated normal in another 9% of the patients. Multivariate analysis showed that small lesion size (<10 mm) was the only predictor of misidentifying the clinically appropriate lesion on conventional magnetic resonance imaging (P<.01).

Conclusions: T2-weighted imaging and FLAIR imaging fail to identify the clinically relevant SPI in almost one quarter of the patients found to have a lesion on DWI. The characteristics of DWI make it well suited for the detection of acute small infarcts. Diffusion-weighted imaging is necessary to consistently define the clinical-anatomical relations in patients initially seen with SPIs.

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Small-penetrator infarcts (SPIs) represent 20% to 25% of all ischemic strokes.1,2 Early identification of these patients is important, as functional outcome with various treatment strategies may vary among stroke subtypes.3,4 In recent years, conventional magnetic resonance imaging (MRI) (ie, T2-weighted imaging [T2WI] and fluid-attenuation inversion recovery [FLAIR] imaging) has been used extensively to detect SPIs.5,6 However, since SPIs lack both extensive edema and mass effect, neither T2WI nor FLAIR imaging can reliably identify whether a particular small lesion was indeed acute and related to the initial symptoms. This is especially important in attributing clinical symptoms to a particular lesion in patients with small vessel disease, who frequently harbor multiple chronic infarcts in the territory of small-penetrator arteries.7,8

Diffusion-weighted imaging (DWI) has high sensitivity and specificity for early detection of ischemic lesions.9,11 In addition, DWI also provides temporal information, as only acute lesions (hours to a few weeks old) are bright when seen on DWI.12,13 Moreover, the increased ratio of signal intensity of ischemic lesion to the background of normal brain on DWI improves the detection of small lesions.12,15 Recently, Singer et al13 reported that DWI revealed an acute lesion within the clinically appropriate brain region in 37 of 39 patients initially seen with a subcortical syndrome; T2WI either was normal or revealed multiple subcortical chronic lesions in 24 of these 39 patients. In the current study, we aimed to determine clinical or radiological predictors associated with misidentification of an SPI as acute using T2WI and FLAIR images in patients with an acute SPI seen on DWI.

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PATIENTS AND METHODS.

During a 20-month period between July 1996 and February 1998, we studied 416 consecutive patients admitted with diagnosis of ischemic stroke confirmed by DWI. Sixty-seven patients had an SPI and were included in this study. Medical history, neurological examination findings, stroke risk factors, stroke causes, and time from symptom onset (last known to be normal) to MRI were recorded in each case. Small–penetrator infarct was defined as an infarct less than 30 mm in maximum diameter in the territory of deep perforator branches of the anterior cerebral artery, middle cerebral artery, posterior cerebral artery, or basilar artery.

Magnetic resonance imaging studies were performed on a 1.5-T magnetic resonance instrument (GE Signa, Waukesha, Wis) with echo-planar capabilities (Advanced NMR Systems, Wilmington, Mass). Trace DWIs were generated by using methods previously described elsewhere.16 Acquisition parameters for DWI included repetition time=6000 milliseconds, echo time of 118 to 154 milliseconds, acquisition matrix=256 × 256, field of view=40 × 20 cm, slice thickness=6 mm, slice gap=1 mm, number of axial slices=17 or 18, maximum b-value of 1221 s/mm², and diffusion gradients applied in 3 or 6 orthogonal directions at an effective strength of 15 mT/m. Fast FLAIR images were acquired with repetition time=10002 milliseconds, echo time=141 milliseconds, an inversion time of 2200 milliseconds, field of view=24 cm, acquisition matrix=256 × 192 pixels, slice thickness=5 mm, slice gap=1 mm, and 1 signal average. Fast spin echo T2WIs were acquired with repetition time=4200 milliseconds, echo time=102 milliseconds, field of view=20 cm, acquisition matrix=256 × 256 pixels, slice thickness=5 mm, slice gap=1 mm, and 1 signal average.

Magnetic resonance images were evaluated by 2 independent examiners (H.A. and P.W.S.) who were blinded to DWI findings, but had access to a brief description of ischemic signs and symptoms (eg, left-sided ataxic hemiparesis). The MR images were examined in a sequential manner, and at each step, the examiners attempted to identify a lesion thought to have caused the symptoms; first based on only T2WI; next based on the FLAIR imaging and T2WI; and last, based on DWI, T2WI, and FLAIR imaging. Maximum lesion diameter seen on T2WI was considered to be consistent with the clinical stroke syndrome in all patients. Mean (±SD) SPI lesion size was 11.9±6.7 mm, and was 10 mm or smaller in 25 patients. Mean (±SD) time from symptom onset to MRI was 50±53 hours (range, 2-336 hours); 27 patients were imaged at 24 hours or less from onset of symptoms. A lesion was called “clinically appropriate” on T2WI in 61 (91%) of 67 patients; in the remaining 6 patients (9%), T2WI was considered normal. A hyperintense lesion called clinically appropriate on T2WI did not have any corresponding lesion on DWI in 9 patients (13%). Multiple bilateral lesions were found in 41 patients (61%) on T2WI. Interrater concordance rate for T2WI evaluations was 89.6% (κ = 0.48).

The comparison between the group of 15 patients in whom T2WI evaluations were inconsistent with DWI and the remaining 52 patients is given in Table 1. Diffusion-weighted imaging showed a hyperintense lesion involving the corona radiata in 22 patients, internal capsule in 25, thalamus in 18, and brainstem in 13. There was a single hyperintense lesion in 60 patients and multiple lesions in 7. The location of at least 1 DWI lesion was thought to be consistent with the clinical stroke syndrome in all patients. Mean (±SD) SPI lesion size was 11.9±6.7 mm, and was 10 mm or smaller in 25 patients. Mean (±SD) time from symptom onset to MRI was 50±53 hours (range, 2-336 hours); 27 patients were imaged at 24 hours or less from onset of symptoms. A lesion was called “clinically appropriate” on T2WI in 61 (91%) of 67 patients; in the remaining 6 patients (9%), T2WI was considered normal. A hyperintense lesion called clinically appropriate on T2WI did not have any corresponding lesion on DWI in 9 patients (13%). Multiple bilateral lesions were found in 41 patients (61%) on T2WI. Interrater concordance rate for T2WI evaluations was 89.6% (κ = 0.48).

The comparison between the group of 15 patients in whom T2WI evaluations were inconsistent with DWI and the remaining 52 patients is given in Table 2. The only predictor of inconsistency between T2WI and DWI was lesion size (P<.001); the DWI lesion could not be identified on T2WI in 13 patients (37%) with a lesion diameter of 10 mm or smaller and in 2 patients (6%) with a lesion diameter larger than 10 mm. Lesion size remained a predictor also in the multivariate analysis (odds ratio=0.117, 95% confidence interval=0.017-0.479, P=.008). Presence and number of vascular risk factors, time from symptom onset to MRI, presence of multiple chronic, hyperintense white matter lesions (MCHWMLs), and lesion location were not significantly different between patients with and without inconsistent images. Multiple, chronic, hyperintense white matter lesions were present in all 9 patients (100%) with lesions misidentified on T2WI, but only in 22 patients (55%) of the remaining 58 patients (P = .01). Diffuse-weighted imaging hy-

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<th>Characteristic</th>
<th>No. (%) of Patients</th>
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<tr>
<td>Demographics</td>
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<tr>
<td>Age, mean ± SD, y</td>
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<td>Sex, M/F</td>
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<td>Workup</td>
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<tr>
<td>MRA*</td>
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<tr>
<td>Carotid ultrasound</td>
<td>32 (48)</td>
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<tr>
<td>MRA or carotid ultrasound</td>
<td>54 (81)</td>
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<td>Medical history</td>
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<tr>
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<td>18 (27)</td>
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<td>Previous stroke</td>
<td>18 (27)</td>
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<td>≥2 Risk factors</td>
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* MRA indicates magnetic resonance angiography.
perintense lesions involved the thalamus (6 cases), internal capsule (5 cases), and corona radiata (4 cases) in patients without congruous T2WIs. An example of a corona radiata lesion that was not identified on T2WI is shown in Figure 1.

Forty-three patients had FLAIR images available for comparison with DWI (Table 2). Results were similar to those of the T2WI evaluations: in 4 patients (9%) FLAIR imaging was considered normal, and in 7 patients (16%), a lesion deemed clinically appropriate on FLAIR imaging was not hyperintense on DWI. Interexaminer concordance rate was 88.4% (κ = 0.38). There were 4 patients in whom FLAIR imaging, but not T2WI, identified the clinically relevant lesion as that seen on DWI. In contrast, no lesion seen on T2WI that overlapped with the DWI hyperintense lesion was missed by FLAIR imaging. Again, the only predictor of FLAIR imaging inconsistency with DWI was the lesion size (P = .004); the DWI lesion was missed in 9 patients (33%) with a lesion diameter of 10 mm or smaller and in 2 patients (12%) with lesions larger than 10 mm. All 7 patients with lesions misidentified as clinically appropriate on FLAIR imaging had MCHWMLs; only 22 (60%) of the remaining 36 patients had MCHWMLs (P = .08). An example of a clinically appropriate lesion that was missed on initial T2WI and FLAIR imaging evaluations is shown in Figure 2.

In acute ischemia, there is a net translocation of water from the extracellular into the intracellular compartments of neurons and glia, ie, cytotoxic edema. Water diffusion is more restricted in the intracellular environment; this is sensed as an increase in DWI signal, within minutes of complete ischemia. In addition to early detection of ischemic injury, DWI also differentiates between acute and chronic infarcts. Initially reduced water diffusion returns to normal after about 2 weeks, causing disappearance of DWI hyperintensity. Chronic infarcts are not hyperintense on DWI.

To our knowledge, our study of 67 patients with a clinically appropriate SPI seen on DWI is the largest series reported in the literature. Our study also demonstrates that conventional MRI is unreliable in revealing the acute lesion in some patients—T2WI failed to identify the acute lesion in 22% (15 of 67 patients), and FLAIR imaging in 26% (11 of 43 patients). Patients with discordant image evaluations more frequently had a small lesion (<10 mm) seen on DWI. More importantly, both T2WI and FLAIR imaging seem to be of limited value in patients with MCHWMLs; all patients with lesions misidentified on T2WI or FLAIR imaging had MCHWMLs.

Multiple chronic, hyperintense white matter lesions are common in patients with ischemic stroke; they were reported in 42% on MRI and in 75% in the pathologic series by Fisher. The presence of MCHWMLs reduce the clinician’s confidence in attributing the patient’s acute clinical symptoms to a particular SPI. In 1 study, 16 of 100 patients initially seen with classic lacunar syndromes were reported to have at least 2 lesions on T2WI, which correlated with the clinical features. In our study, the interexaminer agreement rates were fair to moderate for both T2WI (κ = 0.48) and FLAIR imaging (κ = 0.38). Since only acute-to-subacute infarcts appear hyperintense on DWI, the clinically relevant lesions can be identified with excellent confidence using DWI; accurate lesion localization represents one of the best means of understanding the functions of different subcortical brain regions. Furthermore, our findings question the accuracy of clinicroadiologic correlations done in the pre-DWI era, when physicians had to rely only on conventional MRI.

The rate of detection of SPIs by T2WI and FLAIR imaging shows an inverse relationship with the size of lesion; ie, the smaller the lesion, the more difficult it is
for conventional MRI to identify the SPI seen on DWI. In our study, a small lesion (<10 mm) was less likely to be called acute on blinded ratings if another, larger, chronic lesion was present on T2WI or FLAIR imaging. Small hyper-intensities are easier to see on DWI because of its higher lesion-background signal ratio. In some other patients with small lesions, T2WI and FLAIR imaging were completely normal. Small hyper-intensities are easier to see on DWI because of its higher lesion-background signal ratio.11

Figure 1. A 63-year-old woman with sudden onset left-sided pure motor hemiparesis underwent magnetic resonance imaging 11 hours after symptom onset. Axial T2-weighted imaging (A, B) shows multiple lesions in the right striatum, internal capsule, corona radiata, and periventricular white matter regions. Diffusion-weighted imaging (C, D) identifies only the right corona radiata lesion as acute.
Signal intensity in the ischemic brain regions increases on DWI within 30 minutes of vessel occlusion in animal models. The corresponding signal changes on T2WI and FLAIR imaging become visible only after 8 to 24 hours. In this respect, one would expect to see an improved rate of detection of small lesions by T2WI and FLAIR imaging because they are performed late. However, in our study, time from symptom onset to scanning was not a predictor of missing or misidentifying a lesion on T2WI or on FLAIR imaging. Even if SPIs appeared early on conventional MRI (by 24 hours), it was usually impossible to identify them as the clinically appropriate lesion when there were other coexisting MCHWMLs, because small SPIs lack mass effect or significant edema to characterize them as acute. Therefore, DWI is also valuable beyond the 24-hour time frame in patients with SPIs. This highlights a new aspect of DWI's clinical use, in addition to its well-known indication in the hyperacute detection of cerebral ischemia.

Because most MCHWMLs occur in periventricular regions, an SPI in a periventricular location would more likely be expected to generate an inconsistent result between conventional MRI and DWI. However, infarct location on DWI (such as brainstem, thalamus, or corona radiata) did not differ significantly between the patients with or without inconsistent T2WI or FLAIR images in our study; usually, missed lesions were small (<10 mm) irrespective of location. However, some corona radiata lesions larger than 10 mm were missed, as the example in Figure 1 illustrates.

Our study design did not address the sensitivity and specificity of DWI for SPI. Moreover, it did not permit any direct comparison between DWI and conventional MRI as to whether one test was better than the other. Indeed, such a comparison is difficult with any study design. To mark a new imaging technique as better in a particular clinical indication, one approach might be to study all patients initially seen with the specific clinical syndrome; unfortunately, there is no such unique syndrome in the case of SPIs. At least 21 different syndromes attributable to an SPI have been described using pathologic features or imaging, neither of which can reliably identify an infarction as acute. Five of them, so-called classic lacunar syndromes (ie, pure motor hemiparesis, pure sensory stroke, sensory-motor syndrome, ataxic hemiparesis, and dysarthria–clumsy hand syndrome), are well linked to a lacunar infarct by autopsy studies. However, these clinical syndromes are not present in 29% of patients with a lacunar infarction on either computed tomography or conventional MRI. The positive predictive value of these syndromes for a radiologically proven lacune is 87%. Relying on classic lacunar syndromes for patient selection, in fact, inserts a selection bias and underestimates the true size of this study’s population of interest. Even pathologic examination may not fulfill the role as a criterion standard because patients with SPIs usually do not die of their stroke. Moreover, autopsy examination is limited in the same way as conventional MRI, namely, the examination cannot identify the clinically relevant lesion when there are coexisting MCHWMLs. There is no available or accepted criterion standard test to reliably identify an acute SPI. However, the excellent signal-background ratio that allows detection of very small le-

**Figure 2.** A 42-year-old man with sudden onset right-sided pure motor hemiparesis underwent magnetic resonance imaging 62 hours after symptom onset. Prospective review of axial T2-weighted imaging (A) and fluid-attenuation inversion recovery (B) failed to show the clinically appropriate small (<10-mm) lesion in the left internal capsule, well seen on diffusion-weighted imaging (C). Once the diffusion-weighted imaging lesion is noted, retrospective review of T2-weighted imaging shows a corresponding region of faint signal hyperintensity. On fluid-attenuation inversion recovery there is also a corresponding region of signal hyperintensity, although it is more difficult to distinguish from the bilaterally symmetric increased signal in this area.
sions, and the temporal information that allows marking a lesion as acute, are 2 characteristics that potentially make DWI the most valuable means to detect acute SPI.

The use of DWI in SPI is not confined only to its ability to detect the acute and clinically relevant lesion. Diffusion-weighted imaging also demonstrates the multiplicity of acute, small brain lesions. Seven of the 67 patients in this study had multiple small hyperintense lesions in different vascular territories; in these patients, embolism was thought to be the most likely operative stroke mechanism because simultaneous release of multiple small emboli would be expected to cause multiple lesions on DWI, all hyperintense during the same period. In contrast, if thrombosis owing to hypertensive small vessel disease causes an SPI with some independent probability, then the occurrence of multiple DWI hyperintense lesions—representing separate infarcts of similar age—is expected to be rare. Accordingly, 4 (37%) of our 7 patients with multiple lesions seen on DWI had an identified embolic source as opposed to 19 (32%) of the remaining 60 patients with a single lesion. This did not reach statistical significance in this small sample of patients. However, in a separate study of patients initially seen with a classic lacunar stroke syndrome, the correlation between finding multiple small infarcts seen on DWI and an identifiable embolic source was a statistically significant finding.22

In conclusion, T2WI and FLAIR imaging fail to show the clinically appropriate infarct, as identified by DWI, in almost one quarter of patients with SPIs. Even after the hyperacute phase, DWI promises to be the more useful imaging technique in patients with acute SPIs. The unique ability of DWI to differentiate between acute and chronic lesions provides accurate identification of the clinically relevant lesion(s), which is necessary to consistently establish precise clinical-anatomical correlations.

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REFERENCES

4. TOAST Investigators. Low-molecular weight heparinoid, ORG 10172 (Danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. JAMA. 1998;279:1265-1272.