Diffusion-Weighted MRI in 300 Patients Presenting Late With Subacute Transient Ischemic Attack or Minor Stroke

Ursula G. Schulz, MD; Dennis Briley, MD; Tom Meagher, MD; Andrew Molyneux, PhD; Peter M. Rothwell, PhD

Background and Purpose—Many patients with transient ischemic attack (TIA) or minor stroke present to medical attention after a delay of several days or weeks, at which time it may be more difficult to obtain a clear history and clinical signs may have resolved. Because ischemic lesions on diffusion-weighted MRI (DWI) often persist for several weeks, we hypothesized that adding DWI to a standard protocol with T2-weighted imaging might be useful in the management of patients presenting late.

Methods—We studied consecutive patients with TIA or minor stroke presenting ≥ 3 days after the event. Two independent observers recorded the presence or absence of recent ischemic lesions on 2 different occasions, first with the T2 scan only, and second with T2 and DWI. Each time, with the aid of a written clinical summary, the observers recorded their diagnosis and proposed management.

Results—300 patients (159 men) were scanned at a median of 17 (interquartile range = 10 to 23) days after symptom onset. DWI showed a high signal lesion in 114/164 (70%) minor strokes versus 17/136 (13%) TIs (P < 0.0001). The presence of high-signal lesions on DWI decreased nonlinearly with time since symptom onset (P < 0.0001) and increased with National Institutes of Health Stroke Score (P = 0.038) and with age (P = 0.01). In 90/206 (43.7%) patients with 1 or multiple lesions on T2, DWI helped to clarify whether these were related to a recent ischemic event (79 [48%] strokes; 11 [31%] TIs). Compared with T2 alone, DWI provided additional information in 108 (36%) patients (91 [56%] strokes and 17 [13%] TIs), such as clarification of clinical diagnosis (18 patients, 6%) or vascular territory (28 patients, 9.3%), which was considered likely to influence management in 42 (14%) patients (32 [19%] strokes; 10 [7.4%] TIs).

Conclusions—The clinically useful information available from DWI provides a further justification for an MRI-based imaging protocol in patients with subacute TIA or minor stroke. (Stroke. 2004;35:000-000.)

Key Words: epidemiology ■ magnetic resonance imaging ■ stroke ■ transient ischemic attack

Management guidelines recommend that patients with transient ischemic attack (TIA) and minor stroke are seen as soon as possible after their event. However, many patients delay seeking medical attention, and often there is a further delay before they are seen by specialist stroke services. In these patients, who may be assessed after a delay of several days or even weeks, a clear history may have resolved, and it may be difficult to obtain a definite diagnosis of a cerebral ischemic event or to be certain of the vascular territory or territories involved.

Diffusion-weighted MRI (DWI) is a relatively recent imaging technique, which shows ischemic tissue damage within minutes after onset of the injury, and is therefore mainly used in the investigation of patients presenting acutely with stroke. However, ischemic lesions remain visible for at least 2 weeks after a stroke due to combined effects of the apparent diffusion coefficient (ADC) and T2 shine-through. and DWI detects clinically appropriate ischemic lesions in a high proportion of minor stroke patients when scanned 2 weeks or more after their event. In addition, interobserver agreement for identifying recent ischemic lesions in this patient group is much higher for DWI than for T2-weighted scans. In view of the high sensitivity and reproducibility of DWI in the subacute stage, it may be useful in the routine management of TIA and stroke patients who present late. However, there are no studies of the clinical usefulness of DWI in this group.

In this first-ever large study of DWI in subacute TIA and minor stroke, our aim was to determine whether DWI, when added to T2-weighted imaging, provided additional useful information and influenced management in patients who were assessed in clinical several days or weeks after their event. We also studied whether lesion presence on DWI was associated with any specific clinical characteristics to determine if there are patients in whom it is particularly informative.

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Methods

We prospectively studied consecutive patients referred to a hospital-based TIA and minor stroke clinic from 2000 to 2003 who were considered to have had a probable or definite TIA or stroke. Patients were referred after attending their family doctor and were not therefore seen acutely. TIA and stroke were defined according to World Health Organization criteria. All stroke patients included in the study had a minor nondisabling stroke, that is, they were sufficiently well to remain at home after their event and to attend an outpatient clinic. Baseline clinical data and the National Institutes of Health (NIH) Stroke Score were recorded, and approval was obtained from the local ethics committee.

Two neurologists obtained a detailed history with a standardized questionnaire. This included dates of symptoms, duration and type of symptoms, number of events and details on vascular risk factors, past medical history, and medication. All patients underwent a standardized clinical neurological examination and MR brain imaging on the same day using a 1.5 Tesla Siemens Symphony system with quadrature gradients. The study protocol included a T2-weighted turbo gradient spin echo axial sequence (acquisition time 58 s, repetition time 4000 ms, echo time 95 ms, 19 slices, slice thickness 6.0 mm, matrix 256×256, echos per excitation [EPI-factor]=3) to detect old and potentially new ischemic lesions, hemorrhage and mass lesions, and a diffusion-weighted sequence (acquisition time 68 s, repetition time 2600 ms, echo time 104 ms, 20 slices, slice thickness 6.0 mm, matrix 128×128) to detect recent ischemic lesions. The diffusion gradients were applied along the x, y, and z axis, thus minimizing anisotropic effects, and the DWI sequence was acquired with 3 different b values (b=0, 500, and 1000 s/mm²). A positive DWI scan was defined as high signal on the b1000 image. In cases with a lesion on DWI, we also reviewed the ADC map and noted whether high signal areas on the b1000 image showed low, high, or normal signal on the ADC map when comparing the affected area to the corresponding contralateral area. Furthermore, we assessed whether lesions present on DWI were also present on the T2 image.

In the clinic, all scans were immediately reviewed by a radiologist and, in case of any abnormality not entirely typical of ischemic lesions, further imaging was performed as appropriate (eg, T1-imaging+gadolinium). However, as our study aim was to determine the incremental value of DWI in addition to our standard imaging, we restricted our analysis to the routinely acquired T2 and DW images. In the study, a third neurologist and a neuroradiologist, both with a special interest in cerebrovascular diseases, reviewed the scans jointly on 2 different occasions. Neither observer was involved in the patients’ care, but because our aim was to study the clinical usefulness of DWI, and whether DWI changed patient management, the reviewers had to be aware of the clinical data to be able to comment on patient management and were given a summary of the clinical history and examination. On the first occasion, the observers reviewed the T2-weighted image only and, in a standardized questionnaire, noted their degree of certainty of a clinical diagnosis of stroke or TIA (possible/probable/certain), the presence and number of any infarctions, the affected vascular territory, whether any infarcts were lacunar or nonlacunar, and whether infarcts were recent and consistent with the presenting event. The study neurologist also outlined his management plan (further vascular imaging, further cardiac investigations, and other) on the basis of the clinical presentation and the T2 scan. On the second occasion, at least 4 weeks after the first review, the observers were again presented with the clinical details and replied to the above questions on the basis of the T2 and the DW images. On the second review, the observers also commented whether they felt DWI had added any useful information.

Statistical Analysis

To study the associations between lesion presence on DWI and clinical characteristics, we related the proportion of positive DWI scans to the clinical diagnosis (TIA or minor stroke), baseline clinical characteristics, symptom duration, and time since symptom onset. In stroke patients, we related lesion presence on DWI to the persistence of symptoms and of clinical signs and to the NIH score. We compared proportions with the χ² test and related the NIH score to lesion presence on DWI with the Mann-Whitney test and with ANOVA. All analyses were performed unadjusted and, as appropriate, adjusting for age, sex, and diagnosis in a logistic regression analysis with lesion presence on DWI as the outcome variable of the analysis. In the second part of this study, to determine whether DWI provided additional information when added to T2 imaging, we compared the observers’ assessments of the T2 scans alone with the assessment of T2 and DWI and noted how frequently scan interpretations and proposed management differed. All statistical analyses were performed with SPSS version 10.0.

Results

We studied 300 consecutive patients (159 men, mean SD age=70.7 years [10.8]) with a clinical diagnosis of stroke (n=164, 55%) or TIA (Tables 1 and 2). Median delay from symptom onset to clinic was 17 days (interquartile range=10 to 23, max=90). No patient was scanned within 3 days. During the study period, we saw another 122 patients in whom the clinical diagnosis was not stroke (migraine, n=37); seizure, n=23; transient global amnesia, n=7; syncope, n=18; others, n=37) and who were either not scanned or imaging showed a nonvascular pathology. A further 12 patients with TIA or minor stroke were unsuitable for MRI-scanning. Of the 300 patients who were scanned with the standard cerebrovascular protocol, the research team agreed with the diagnosis of TIA or stroke on the basis of the clinical summary in 91% (κ=0.76, 95% CI=0.69 to 0.82; P<0.0001).

DWI and Clinical Characteristics

A high signal lesion consistent with a recent cerebral infarct was present on DWI in 131 (43.7%) patients, and in all of these the location of the lesion was compatible with the clinical presentation. In 23 (17.6%) patients, the ADC was increased compared with the contralateral side, in 65 (49.6%) there was no difference compared with the corresponding contralateral area, and in 43 (32.8%) the ADC was reduced. Figure 1 shows the proportion of high signal lesions on DWI with a corresponding low or with an increased ADC in relation to time since event. The proportion of lesions with a high ADC increased with time, but even 4 weeks or more after the initial event, there were 6 patients with DWI lesions with a corresponding low ADC. We found a strong negative association between time since symptom onset and lesion presence on DWI (Table 3), although only in stroke patients (odds ratio=0.94; 95% CI=0.91 to 0.97; P<0.0001).

A clinical diagnosis of stroke was the strongest predictor of lesion presence on DWI: 69.5% of strokes versus 12.5% of TIAs. Table 2. A motor deficit or dysarthria were also associated. In the stroke patients, lesion presence was related to persistence of symptoms: 76/98 (67.6%) versus 38/66 (57.6%) patients whose symptoms had resolved (P=0.006). Similarly, DWI was positive more frequently in stroke patients with persisting signs: 56/71 (78.9%) versus 58/93 (62.4%), P=0.023. NIH scores of the stroke patients ranged from 0 to 9, and 26 patients had a score >3 (NIH=4 in 14, 5 in 5, >5 in 7). Lesion presence was associated with a higher NIH score (P=0.037, Table 1). These associations were still present after adjusting for age and sex (Table 3). There was
no association of lesion presence with stroke subtype according to the Oxfordshire Community Stroke Project (OCSP) classification.13

Treatment for hypercholesterolemia, leukoaraiosis, and atrial fibrillation were positively associated with a lesion on DWI, and a history of a previous TIA was negatively associated. However, these associations were weakened or no longer significant after adjustment for age, sex, and diagnosis. Increasing age was the only patient characteristic strongly associated with lesion presence on DWI before and after adjustment.

### TABLE 2. Baseline Characteristics of All 300 Patients Presenting With a TIA or Minor Stroke and Separately for Stroke and TIA Patients

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Stroke Patients</th>
<th>TIA Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=300)</td>
<td>DWI+ (n=114)</td>
<td>DWI− (n=186)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>159 (53.0%)</td>
<td>80 (59.2%)</td>
<td>79 (62.7%)</td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>70.7±10.8</td>
<td>72.5±10.3</td>
<td>68.5±10.8</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>154 (51.3%)</td>
<td>75 (62.1%)</td>
<td>79 (64.4%)</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>29 (9.7%)</td>
<td>14 (11.5%)</td>
<td>15 (12.1%)</td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>49 (16.3%)</td>
<td>25 (20.7%)</td>
<td>24 (19.7%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>58 (19.3%)</td>
<td>25 (21.7%)</td>
<td>33 (28.1%)</td>
</tr>
<tr>
<td>Prior TIA</td>
<td>44 (14.7%)</td>
<td>20 (16.7%)</td>
<td>24 (19.7%)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>28 (9.3%)</td>
<td>13 (14.3%)</td>
<td>15 (12.1%)</td>
</tr>
<tr>
<td>History of IHD</td>
<td>62 (20.7%)</td>
<td>37 (25.6%)</td>
<td>25 (21.7%)</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>25 (8.3%)</td>
<td>16 (12.1%)</td>
<td>9 (7.6%)</td>
</tr>
<tr>
<td>Leukoaraiosis*</td>
<td>164 (55.6%)</td>
<td>84 (66.5%)</td>
<td>80 (57.4%)</td>
</tr>
<tr>
<td>Any lesion on T2</td>
<td>Single</td>
<td>45 (15.0%)</td>
<td>29 (21.2%)</td>
</tr>
<tr>
<td></td>
<td>Multiple</td>
<td>161 (53.7%)</td>
<td>91 (63.5%)</td>
</tr>
</tbody>
</table>

Absolute numbers and percentages are given for the entire cohort and separately for patients with and without a lesion on DWI (column percentages). IHD indicates ischemic heart disease. P shows whether the characteristics differed significantly between patients with and without a lesion on DWI in the unadjusted analysis.

*On treatment for this condition.

†Significant differences (P<0.05).
adjustment (Tables 2 and 3). However, we also found a trend
for stroke patients to be older than TIA patients (mean SD,
71.1 [10.4] versus 69.6 [11.2] years; \( P = 0.09 \)), and there was
a weak but significant positive correlation between age and
NIH score (Spearman \( r = 0.13, P = 0.03 \)). Because diagnosis
and stroke severity were also both positively associated with
lesion presence on DWI, they may partially explain the
association between DWI appearance and age.

### TABLE 3. Logistic Regression Analysis of the Association
Between Lesion Presence on DWI and Clinical Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis stroke</td>
<td>16.95 (9.02–31.84)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.01 (0.57–1.79)</td>
<td>0.980</td>
</tr>
<tr>
<td>Age, per 10 y</td>
<td>1.71 (1.29–2.28)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Days since onset</td>
<td>0.97 (0.95–0.99)</td>
<td>0.019†</td>
</tr>
<tr>
<td>NIH stroke score</td>
<td>1.24 (1.00–1.53)</td>
<td>0.047†</td>
</tr>
<tr>
<td>Persisting symptoms</td>
<td>2.66 (1.31–5.41)</td>
<td>0.007†</td>
</tr>
<tr>
<td>Persisting signs</td>
<td>2.42 (1.17–5.02)</td>
<td>0.018†</td>
</tr>
<tr>
<td>Left brain side affected</td>
<td>1.13 (0.59–2.20)</td>
<td>0.725</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>1.04 (0.58–1.84)</td>
<td>0.903</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>0.98 (0.40–2.44)</td>
<td>0.972</td>
</tr>
<tr>
<td>hypercholesterolemia*</td>
<td>0.58 (0.26–1.30)</td>
<td>0.186</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.91 (0.89–4.13)</td>
<td>0.099</td>
</tr>
<tr>
<td>Prior TIA</td>
<td>0.42 (0.18–0.98)</td>
<td>0.046†</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>0.78 (0.31–1.98)</td>
<td>0.603</td>
</tr>
<tr>
<td>History of IHD</td>
<td>0.67 (0.33–1.37)</td>
<td>0.274</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.48 (1.08–11.16)</td>
<td>0.036†</td>
</tr>
<tr>
<td>Leukaraiosis</td>
<td>1.39 (0.71–2.70)</td>
<td>0.334</td>
</tr>
<tr>
<td>Any lesion on T2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>7.95 (2.84–22.23)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Multiple</td>
<td>4.99 (2.27–11.01)</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

The table shows the odds ratios (95% CI) of a lesion being present on DWI vs a lesion not being present related to each shown characteristic. The analyses were performed for the entire patient cohort, and the analyses were adjusted for age, sex, and diagnosis. OR indicates odds ratio; IHD, ischemic heart disease.

*On treatment for this condition.
†Significant differences.
posterior circulation events would either not have been referred, or, in case of a carotid stenosis being identified, this would have been regarded as incidental. Four patients, whose DWI scans showed multiple acute lesions, would now have been referred for additional more detailed investigations to identify causes of systemic embolism. In 16 patients, in whom either the T2 scan had been normal or the history had not been entirely typical of a cerebral ischemic event, the positive DWI scan resulted in a definite diagnosis and full investigation and treatment. Overall DWI would have resulted in a change of management in 42 (14.0%) patients [32 (19.5%) strokes and 10 (7.4%) TIAs].

**Discussion**

We found that in patients with subacute TIA and stroke, lesion presence on DWI mainly depended on the characteristics of the ischemic event rather than the patient. We also found that DWI added useful clinical information and influenced management in a significant proportion of patients.

Many patients still had a lesion several weeks after the event. The occurrence of new, sometimes asymptomatic, lesions after an ischemic event has been reported,\(^14\) and because of the cross-sectional design of our study, we cannot be entirely certain that some of the lesions that we identified were not more recent than we supposed. To be absolutely certain of the age of the lesions, a follow-up study from symptom onset would have been required. However, this would have required a different patient population and the results might not have been generalizable to patients who present late. Additional lesions, which were clinically silent, would only pose a diagnostic problem if the original lesion resolved and if they affected a different vascular territory than the original lesion. From a clinical point of view, it is unlikely that they would lessen the usefulness of DWI, because their appearance would still confirm the diagnosis of a cerebral ischemic event and help to plan further management. Finally, although DWI appearances have been reported to normalize 2 weeks after stroke,\(^15\) there are now several studies suggesting that high signal on DWI may persist for much longer.\(^8,9,10\)

In most patients with a lesion on DWI, the ADC was increased or normal, although it was still low \(\geq 4\) weeks after the event in 6 patients. The DWI signal is influenced by the ADC and T2 effects, and the contribution of each of these to the DWI signal at different time points is complex. In the first few days after an ischemic event, high signal on DWI is mainly caused by a low ADC. However, the ADC normalizes after \(\approx 10\) days, and it is increased in the chronic phase.\(^8,16,17\) High signal on DWI in the subacute and chronic phase is thought to be mostly caused by T2 shine-through. Although a persistently low ADC has been reported previously,\(^8\) it is unusual for the ADC to be low several weeks after an ischemic event, as was the case in our six patients. Although consistent with the original clinical presentation, the lesions may have been caused by a more recent clinically silent event. In this case, DWI would still help to make a diagnosis of cerebrovascular disease. However, a low ADC after several weeks is unusual, and this finding should be interpreted with caution.

The lesion rate for TIA patients in our study was low. This contradicts the findings of studies in which TIA patients were scanned within a few hours\(^18,19\) or even within a few days\(^20,21\) after symptom onset. However, it has been shown that lesions on DWI may be reversible.\(^15\) In our study, patients were scanned later than in the previous studies, and it is likely that the low rate of positive scans in TIA patients in our study reflects lesion reversibility on DWI. One other possible cause of a low DWI lesion rate in TIAs is misdiagnosis, because interobserver agreement for the diagnosis of TIA is only
moderate. However, in our study, agreement between our clinicians and the study observers was good, and misdiagnosis is unlikely to have contributed significantly to the low DWI lesion rate.

Increasing age was strongly associated with lesion presence on DWI. The only other study of age and DWI reported a trend for the ADC to increase more quickly in older patients, which should result in a more rapid normalization of the DWI appearance. However, our findings may partly be confounded, because older patients were more likely to have had a stroke than a TIA and tended to have more severe strokes than younger patients, although the association between DWI lesion presence and age appeared to be independent of these factors. One possible explanation is that older patients may have a relatively larger contribution of T2 effects to their DWI appearance, which may reflect age-dependent differences in repair mechanisms after stroke. T2 signal reflects increased total water content, and decreased glial activity after stroke has been reported in older patients, which might result in more marked cystic infarct transformation.

Lesion presence on DWI was weakly associated with presentation with dysarthria or motor symptoms. The association with motor symptoms is the only consistent finding in previous reports, otherwise, symptom type does not appear to be associated with lesion presence.

In 11 patients, DWI helped to identify lesions which were missed by the observers when reviewing the T12-scan alone. The lesion was, in fact, visible (although indistinct) on T2 in retrospect in 6 patients, but in 5 patients no lesion was identifiable on T2. This situation has been reported in acute stroke, but it is difficult to explain in the subacute stage. At this point, most of the high signal on DWI should be caused by T2 shine-through, which should also be visible on the T2 scan. One possible cause is “fogging,” that is, the temporary disappearance of the lesion 2 to 3 weeks after the ischemic event. It is also possible that the lesions on DWI were caused by new asymptomatic lesions, which were not yet visible on the T2 scan. However, this is unlikely to have been the case in all 5 patients. More likely, because all 5 lesions were small and were only seen on 1 slice, it is possible that patient movement could have resulted in the lesions being missed on T2. Irrespective of the explanation, one important benefit of DWI is that ischemic lesions are much more obvious than on T2 imaging.

DWI is helpful in the management of acute stroke patients. We have shown that it is also useful at the subacute stage, providing useful information over and above T2 imaging in 36% of patients (55.5% strokes and 12.5% TIAs), most commonly by increasing certainty of diagnosis and of vascular territory. As in acute stroke, the additional certainty is likely to be particularly helpful to less experienced medical staff. In relatively experienced hands in our study, DWI would have influenced clinical management in 20% of strokes and 7% of TIAs. Although this is a subjective judgment and may depend on local policies, (eg, whether carotid imaging is only done in patients with anterior circulation events), it is unlikely that the results would be very different in other centers.

We confined our analysis of usefulness to patients with positive DWI scans. Potentially, negative DWI scans might also be helpful, at least in terms of diagnostic probabilities, particularly in patients presenting with an acute stroke-like neurological deficit. In this case, a normal DWI scan would reduce the probability of a cerebral ischemic event. In our cohort, there were 2 such patients. However, dogmatic interpretation is not possible, because false-negative DWI scans have been reported even in acute stroke.

Conclusion

DWI provides clinically useful information that affects management in a significant proportion of patients presenting late with TIA or minor stroke. The use of DWI is an additional justification for an MRI-based imaging protocol in patients presenting with subacute cerebrovascular events.

References

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