Systematic Review of Associations Between the Presence of Acute Ischemic Lesions on Diffusion-Weighted Imaging and Clinical Predictors of Early Stroke Risk After Transient Ischemic Attack

Jessica N.E. Redgrave, MRCP; Shelagh B. Coutts, MD; Ursula G. Schulz, DPhil; Dennis Briley, MD; Peter M. Rothwell, PhD

Background and Purpose—Early risk of stroke after a transient ischemic attack can be reliably predicted with risk scores based on clinical features of the patient and of the ischemic event, but it is unclear how these features correlate with findings on brain imaging.

Methods—We performed a systematic review of the literature and identified all previous studies which reported patient characteristics and the nature of transient ischemic attack symptoms in relation to appearances on diffusion-weighted imaging (DWI). We then performed a meta-analysis of the associations between the components of the risk scores and positive DWI. Authors were contacted for additional unpublished data.

Results—Nineteen studies were identified by the systematic review, and additional unpublished data were obtained from 11 of these studies. On meta-analysis, several components of the risk scores were associated with positive DWI, including symptom duration ≥60 minutes (13 studies, odds ratio [OR], 1.50; 95% CI, 1.16 to 1.96; P = 0.004), dysphasia (9 studies, OR, 2.25; 95% CI, 1.57 to 3.22; P < 0.001), dysarthria (8 studies, OR, 1.73; 95% CI, 1.11 to 2.68; P = 0.03) and motor weakness (9 studies, OR, 2.20; 95% CI, 1.56 to 3.10; P < 0.001). However patient age, sex, hypertension and diabetes were not associated with the presence of DWI lesions. From an etiologic perspective, atrial fibrillation (9 studies, OR, 2.75; 95% CI, 1.78 to 4.25; P < 0.001) and ipsilateral ≥50% carotid stenosis (10 studies, OR, 1.93; 95% CI, 1.34 to 2.76; P < 0.001) were associated with positive DWI.

Conclusions—Presence of acute ischemic lesions on DWI correlates with several clinical features known to predict stroke risk after transient ischemic attack. Large studies (sample size >1000) will therefore be required to determine the independent prognostic value of DWI and its interactions with these clinical characteristics. (Stroke. 2007;38:1482-1488.)

Key Words: diffusion-weighted imaging ■ prognosis ■ transient ischemic attack

The risk of stroke after a transient ischemic attack (TIA) is up to 10% in the first 7 days.1–4 Risk scores (eg, ABCD and California score) have been developed to help identify patients at highest early risk of stroke after a TIA.5,5 These scores incorporate age, blood pressure, diabetes, and the nature of ischemic symptoms and are intended for initial triage in primary care and for public education about the characteristics of high-risk events. However, additional potentially prognostic information is available once patients have presented to medical attention and been investigated, such as data on carotid stenosis and acute ischemia on brain imaging. Prognostic scores for use in secondary care clearly need to incorporate such information.

Diffusion-weighted MR-brain—imaging (DWI) is highly sensitive to ischemic changes, and a substantial proportion of TIA patients have acute ischemic lesions on DWI.6,7 Recent studies have suggested that TIA patients with positive DWI are at high early risk of stroke.8,9 In order to plan appropriately powered studies to develop prognostic scores that would incorporate the results of brain imaging, we need to understand how the presence of DWI lesions in patients with TIA relates to the clinical features in the existing risk scores and to other prognostic variables, such as atrial fibrillation and carotid stenosis.10,11 We therefore performed a systematic review of studies which reported clinical features in relation to DWI appearances after a TIA and performed a meta-anal-
Summary of Studies in Systematic Review

<table>
<thead>
<tr>
<th>Author, Reference</th>
<th>n</th>
<th>Consecutive?</th>
<th>Mean/SD Age</th>
<th>Male, %</th>
<th>DWI Positive (%)</th>
<th>Delay to DWI</th>
<th>≥60-min Symptom Duration, n (%)</th>
<th>Positive Predictors of Acute Ischemic DWI Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamal et al15</td>
<td>28</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>13 (46)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Winbeck et al16</td>
<td>60</td>
<td>NR</td>
<td>61.6</td>
<td>68</td>
<td>18 (30)</td>
<td>&lt;24 h</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Marx et al20</td>
<td>14</td>
<td>Yes</td>
<td>70.7</td>
<td>57</td>
<td>4 (29)</td>
<td>&lt;24 h</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Coutts et al21</td>
<td>106*</td>
<td>NR</td>
<td>NR</td>
<td>65</td>
<td>41 (38)</td>
<td>&lt;24 h</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Kidwell et al22</td>
<td>42</td>
<td>Yes</td>
<td>72</td>
<td>60</td>
<td>20 (48)</td>
<td>&lt;24 h</td>
<td>NR</td>
<td>Greater mean duration of symptoms</td>
</tr>
<tr>
<td>Ay et al23</td>
<td>87</td>
<td>Yes</td>
<td>73 (13)</td>
<td>53</td>
<td>36 (41)</td>
<td>&lt;24 h</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Crisostomo et al24</td>
<td>78</td>
<td>NR</td>
<td>67 (15)</td>
<td>55</td>
<td>16 (21)</td>
<td>&lt;24 h</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Cucchiara et al25</td>
<td>61</td>
<td>No</td>
<td>58.5 (15.3)</td>
<td>44</td>
<td>15 (25)</td>
<td>NR</td>
<td>NR</td>
<td>Unilateral weakness vs patients with no weakness or speech disturbance (OR, 6.29; 95% CI, 1.16–3.48), P=0.03</td>
</tr>
<tr>
<td>Engelter et al26</td>
<td>40</td>
<td>Yes</td>
<td>61 (10.5)</td>
<td>50</td>
<td>14 (35)</td>
<td>&gt;24 h</td>
<td>NR</td>
<td>Duration ≥60 mins</td>
</tr>
<tr>
<td>Ay et al27</td>
<td>57</td>
<td>Yes</td>
<td>67.7</td>
<td>49</td>
<td>27 (47)</td>
<td>&gt;24 h</td>
<td>NR</td>
<td>Previous non stereotype TIA (OR= 8.28, P=0.05), motor symptoms (OR=4.75, P=0.008), known etiology</td>
</tr>
<tr>
<td>Lamy et al28</td>
<td>98</td>
<td>Yes</td>
<td>60.6 (15.4)</td>
<td>57</td>
<td>34 (35)</td>
<td>&gt;24 h</td>
<td>NR</td>
<td>Duration ≥60 min, aphasia, motor deficits</td>
</tr>
<tr>
<td>Nakamura et al29</td>
<td>18</td>
<td>Yes</td>
<td>70.6</td>
<td>88</td>
<td>9 (50)</td>
<td>&gt;24 h</td>
<td>NR</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Purroy et al30</td>
<td>83</td>
<td>NR</td>
<td>66.4 (12.4)</td>
<td>54</td>
<td>27 (33)</td>
<td>&gt;24 h</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Inatomi et al31</td>
<td>129</td>
<td>Yes</td>
<td>67 (14)</td>
<td>68</td>
<td>57 (44)</td>
<td>&gt;24 h</td>
<td>NR</td>
<td>Higher cortical dysfunction (P&lt;0.001), duration &gt;30 min</td>
</tr>
<tr>
<td>Rovira et al32</td>
<td>58</td>
<td>Yes</td>
<td>60</td>
<td>91</td>
<td>39 (67)</td>
<td>&gt;24 h</td>
<td>NR</td>
<td>Greater mean duration of symptoms</td>
</tr>
<tr>
<td>Kastrup et al33</td>
<td>42</td>
<td>NR</td>
<td>69 (9)</td>
<td>79</td>
<td>19 (45)</td>
<td>&gt;24 h</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Takayama et al34</td>
<td>19</td>
<td>Yes</td>
<td>70.8</td>
<td>NR</td>
<td>7 (37)</td>
<td>NR</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Restrepo et al35</td>
<td>22</td>
<td>NR</td>
<td>62 (14)</td>
<td>50</td>
<td>12 (55)</td>
<td>NR</td>
<td>14 (64)</td>
<td>None</td>
</tr>
<tr>
<td>Schultz et al36</td>
<td>200</td>
<td>Yes</td>
<td>71.2 (11.5)</td>
<td>53</td>
<td>31 (16)</td>
<td>&gt;24 h</td>
<td>NR</td>
<td>Greater mean age (P=0.02) and symptom duration (P=0.02), atrial fibrillation (P=0.002), dysarthria (P=0.005)</td>
</tr>
</tbody>
</table>

NR indicates not reported.
*Unpublished data on 41 patients supplied by authors.

Method

We searched Medline using index terms (‘TIA’ OR ‘transient ischemic’ OR ‘transient ischaemic’: AND ‘DWI’ OR ‘diffusion weighted’ OR ‘apparent diffusion’ OR ‘ADC’) limited to studies in humans (last search on October 31, 2006). Studies were included if baseline patient characteristics or the nature of TIA symptoms were reported separately for patients with positive versus negative DWI or if these data might have been available from the authors. We also hand-searched the bibliographies of the retrieved articles and the contents pages (1999 to present) of the 2 most frequent journals identified by the electronic search.

For each study, we recorded inclusion and exclusion criteria, the definitions of TIA and a positive DWI scan, whether a neurologist had assessed the patients, whether all DWI lesions were symptomatic, details of the scan protocol, and the mean time interval between TIA and DWI. The proportion of patients with positive DWI and the prevalence of positive DWI in relation to components of the risk scores (age, blood pressure, diabetes, nature and duration of ischemic symptoms) and likely TIA etiology (atrial fibrillation, ≥50% ipsilateral carotid stenosis) were recorded. We contacted authors to request unpublished data if these data were not available in the published article. We also included unpublished data from our own study of patients attending a specialist clinic, which currently includes 200 patients with TIA.12,13

Analysis

Odds ratios were calculated for positive versus negative DWI for each clinical feature under investigation, and estimates from individual studies were combined using the Mantel–Haenszel method. If there were no patients in one of the subgroups, 0.5 was added to all 4 cells in the 2×2 table to enable graphic representation and CI estimation.14 Heterogeneity between estimates from individual studies was determined (χ² test). Results were stratified according to the delay between TIA and DWI (<24 hours versus ≥24 hours). SPSS (version 12.0) and in-house meta-analysis software were used for analysis.

Results

Sixty-five potentially relevant articles were identified, of which 19 met our inclusion criteria,6–9,12,15–28 including two Japanese studies which were translated into English. The most frequent journals of publication were Stroke (n=5) and American Journal of Neuroradiology (n=3). The studies were published between 1999 and 2006 and are summarized in the Table. Twelve studies stated that the patients were...
recruited consecutively,6,12,15,17–19,25,27 usually from stroke units, acute hospital admissions, or neurology out-patients. All studies used the TIA definition of “ischemic symptoms lasting <24 hours.” Two studies excluded posterior circulation events,16,20 and one study excluded anterior circulation events.20 Four studies excluded patients if the delay to scan was above a certain threshold (6 hours,15 24 hours,16 3 days,7 and 14 days19). In 13 studies, a vascular neurologist made the diagnosis of TIA, but the specialty of the attending physician was not stated in the remaining 6 studies.16,17,19,20,23,25

A magnet strength of 1.5 T was used in all but two studies (1.0 T23 and 3.0 T3). Slice thickness was 4 to 7 mm in 11 studies,6,7,9,12,15–17,19,21,25,27 3 mm in one study20 and not stated in the remaining studies. Interslice gap was zero in 3 studies,6,15,27 1 to 2 mm in 6 studies16,17,19,21,25 and >2 mm in one study.7 A positive scan was usually defined as increased signal on DWI, but 10 studies stated that lesions must also have reduced apparent diffusion coefficient.6–8,16,18,19,24–27

The median number of patients per study was 61 (range 14 to 129) and the median mean delay to scan was 37 hours (Table; <24 hours in 6 studies,6–8,16,20,25 >24 hours in 9 studies9,12,17–19,21–23,27 and not stated in 4 studies15,24,26,28). The proportion of patients with positive DWI ranged from 16% to 67% across the 19 studies (Table). Seven studies stated that all patients with positive DWI had lesions that were in an appropriate vascular territory for the presenting symptoms,17,18,20,22,23,25,26 4 studies included a minority of patients with potentially asymptomatic lesions8,12,21,27 and the remaining 8 studies did not give these data.

Several studies recorded additional details of the DWI lesions (eg, size, number and location), but with the exception of one study,17 only the presence or absence of a DWI lesion(s) were reported in relation to clinical characteristics. Rovira et al17 reported no association between DWI lesion size and symptom duration in 39 patients.

There were no associations between positive DWI (Figure 1) and age ≥60 (9 studies, odds ratio [OR], 1.26; 95% CI, 0.91 to 1.75; P=0.24), male sex (13 studies, OR, 1.14; 95% CI, 0.88 to 1.48; P=0.37), previous hypertension (usually defined as being on treatment; 14 studies, OR, 0.90; 95% CI, 0.69 to 1.18; P=0.51), current raised blood pressure (>160 systolic or >95 diastolic18,22 or >140 or ≥9016,26,27; 8 studies, OR, 1.08; 95% CI, 0.79 to 1.47; P=0.71) or diabetes (13 studies, OR, 0.82; 95% CI, 0.57 to 1.20; P=0.38). However, dysphasia (9 studies, OR, 2.25; 95% CI, 1.57 to 3.22; P<0.001), motor weakness (9 studies, OR, 2.20; 95% CI, 1.56 to 3.10; P<0.001) and dysarthria (8 studies, OR, 1.73; 95% CI, 1.11 to 2.68; P=0.03) were strongly associated with positive DWI (Figure 2). Duration ≥60 minutes was also positively associated with DWI lesions (13 studies, OR, 1.50; 95% CI, 1.16 to 1.96; P=0.004; Figure 2) as were atrial fibrillation (9 studies, OR, 2.75; 95% CI, 1.78 to 4.25; P<0.001) and ipsilateral carotid stenosis ≥50% (10 studies, OR, 1.83; 95% CI, 1.26 to 2.65; P=0.003; Figure 3).

Discussion

Our meta-analysis has shown that certain clinical features which are known to predict a high early risk of stroke after a TIA are also associated with the presence of acute ischemic lesions on DWI. In general, it was the characteristics of the TIA (eg, duration, motor weakness, dysphasia, and the underlying etiology [carotid stenosis and atrial fibrillation] rather than traditional vascular risk factors (age, sex, diabetes, hypertension, and blood pressure) that were associated with a positive DWI.

There are several possible explanations for the associations between patient and event characteristics and positive DWI. Clinical diagnosis of TIA is not completely reliable,30 and some patients with an apparent TIA will have a nonvascular etiology. Therefore, the presence of a potentially causal vascular pathology, such as AF or carotid stenosis, makes it more likely that the diagnosis of TIA was correct—and hence the DWI is positive. However, it is also possible that AF and carotid stenosis might be associated with a more severe ischemic insult, which could also increase the rate of positive DWI. In the case of carotid stenosis, reduced perfusion may alter the diffusion properties of brain tissue on the ipsilateral side31 and might also influence the temporal evolution of DWI lesions as well as susceptibility to ischemia in the first place. It is uncertain why motor weakness and dysphasia are associated with a positive DWI. Again, it is possible that they simply indicate a greater likelihood of a correct diagnosis of TIA although in most of the studies in the meta-analysis the diagnosis of TIA was made by a vascular neurologist. It is also theoretically possible that some cerebral locations are more susceptible to infarction than others (eg, attributable to reduced collateral circulation) and that this relates to presenting symptoms.

Three studies have reported prognostic data for TIA patients8,9,28 in relation to DWI appearances at baseline. However, all 3 were relatively small and were not powered to determine the independent prognostic value of DWI lesions. Cucchiara et al studied 61 patients but identified only 2 strokes at 90-day follow-up.28 Purroy et al8 (83 patients) found that patients with both a positive DWI and a symptom duration >60 minutes were at greater risk of recurrent TIA or stroke at 90-days than patients with neither (OR, 5.02; 95% CI, 1.37 to 18.3; P=0.02). Coulls et al9 (106 patients) found that TIA patients with both a positive DWI and intracranial vessel occlusion were more likely to have recurrent stroke at 90 days than patients with neither (OR, 8.9; 95% CI, 1.6 to 49.6; P=0.01).

It has been proposed that TIA be redefined as ischemic symptoms lasting <1 hour without evidence of acute infarction.33 This stems from the fact that the majority of TIA patients resolve within 1 hour and a significant proportion of patients with TIA have infarcts on brain imaging. We have found that symptom duration ≥60 minutes is associated with the presence of acute ischemic lesions on DWI in patients with TIA. However, positive DWI is also associated with dysphasia, dysarthria, weakness, atrial fibrillation and large artery atherosclerosis, all of which have prognostic significance after a TIA.30,31 Therefore, a risk stratification tool which incorporates these other important clinical features as well as symptom duration is likely to be most useful in the prognostication of patients with TIA.

In all 19 studies, the proportion of TIs lasting ≥60 minutes (30% to 83%) was greater than that found in the general population of patients with TIA,34 suggesting that there may have been some selection bias. For example,
studies which scanned patients acutely generally recruited patients from the emergency department and may have included patients with more severe symptoms than studies which recruited from outpatient clinics and tended to scan patients after a delay. However, studies which scanned late may also have been subject to bias because TIA patients with early recurrent stroke were excluded, some silent recurrent lesions may have been included, and some very transient

Figure 1. Patients characteristics. Meta-analysis of associations between clinical characteristics and positive DWI (u/d=unpublished data). Probability values given for the significance (sig) and heterogeneity (het) of pooled odds ratios.
lesions on DWI may have been missed. Another source of heterogeneity might be variation in the definition of ‘positive DWI’ and whether lesions in a vascular territory different to that expected from the clinical history were included. However, several studies did not provide all these data.

Extrapolation from studies in patients with acute stroke suggests that DWI parameters other than simply the presence or absence of acute ischemic lesions may be associated with prognosis in patients with TIA. For example, there is some evidence that lesion size or volume is associated with worse outcome.

Figure 2. Characteristics of the TIA. Meta-analysis of associations between clinical characteristics and positive DWI (u/d=unpublished data). Probability values given for the significance (sig) and heterogeneity (het) of pooled odds ratios.
short-term outcome after ischemic stroke\textsuperscript{19,36} although this association may not be independent of age and stroke severity.\textsuperscript{37} In addition, multiple acute ischemic lesions on DWI in patients with acute stroke, often indicating embolic etiology\textsuperscript{38,39} are associated with recurrent silent DWI lesions on follow-up.\textsuperscript{35,40} In this review, the majority of studies only reported clinical or follow-up data in relation to DWI lesion presence, and the prognostic relevance of size and pattern of lesions on DWI after a TIA is unclear.

Large studies of DWI in patients with TIA are now required in order to reliably determine the prognostic value of all of the above DWI characteristics and to afford sufficient power to determine what they add to established clinical risk factors for early stroke.\textsuperscript{4,5} Given the number of potentially prognostic clinical and DWI characteristics, and their non-independence and potential for complex interaction as identified in this review, sample sizes of at least 1000 patients with acute TIA are likely to be required. Indeed, to determine the independent predictive value of 10 variables, and to allow for several interaction terms, a sample size of 2000 is required based on an expected event rate of 10\% at 30 days.\textsuperscript{41}

In conclusion, several clinical characteristics with proven prognostic significance are associated with the presence of acute ischemic lesions on DWI after TIA. Future studies of DWI will need to be appropriately powered to adjust for clinical features and the underlying etiology in order to determine how best to incorporate DWI into clinical risk scores.

Figure 3. Etiology of the TIA. Meta-analysis of associations between clinical characteristics and positive DWI (u/d=unpublished data). Probability values given for the significance (sig) and heterogeneity (het) of pooled odds ratios.

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None.

References


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