Original Article

Clinical characteristics and outcomes in patients with lesion-positive transient ischemic attack

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Transient ischemic attack (TIA) indicates high risk for major stroke and is considered a medical emergency. Diffusion-weighted imaging (DWI) enables detection of acute ischemic lesions. The clinical significance of DWI positive lesions in TIA is obscure and its prevalence, clinical features are not established. Therefore, we performed a clinical, etiological and prognostic analysis through a cross-sectional analysis of 235 TIA patients, grouped according to presence of DWI lesion. Clinical features, underlying risk factors for stroke, outcome and rate of recurrence were analyzed. 3 months follow-up of modified Rankin Scales (mRS) were done with telephone survey. DWI positive lesions were present in 14.0% of patients. Etiological factors significantly associated with DWI lesions in TIA patients were male sex ($p = 0.038$), stroke history ($p = 0.012$) and atrial fibrillation ($p < 0.001$). Presence of at least one medium or high risk of cardioembolism from TOAST classification were not associated with lesions when excluding association to atrial fibrillation ($p = 0.108$). Clinical features showed no significant difference. Whether the patients had lesion-positive DWI was not related to an increase in mRS score during the hospital stay or at the 3-month follow-up after discharge. Future studies should include multi-center samples with large numbers, considering each unique medical environment. Routine acquisition of follow-up DWI for proper evaluation of the tissue-based definition of TIA should also be considered.

Key words: transient ischemic attack, diffusion weighted imaging, cardioembolism, stroke, atrial fibrillation

Introduction

Individuals who experience a transient ischemic attack (TIA) are at high risk of stroke [1–3]. The stroke incidence is ~10% at 90 d after TIA and ~15% at 1 year after TIA [1]. The 1988 World Health Organization (WHO) criteria define TIA as focal neurological symptoms lasting less than 24 h with no clear non-vascular cause [4]. Diffusion-weighted imaging (DWI) enables detection of acute ischemic lesions [5, 6]. The clinical significance of the presence of such lesions in patients with TIA has gained recent attention, as acute ischemic lesions are reportedly independently predictive of stroke [7–10]. Therefore, a tissue-based definition of TIA (i.e., focal neurological symptoms lacking acute ischemic lesions) is emerging [11–14].Clinical features of patients with lesion-positive DWI are unclear, and findings vary [15–21]. Clinical and etiological characteristics of patients with TIA and lesion-positive DWI have been examined. A systematic review of 19 studies (combined n = 1,242; individual studies, median n = 58, range n = 14–200) concluded that atrial fibrillation and ipsilateral carotid stenosis of >50% were associated with lesion-positive DWI, whereas age, sex, hypertension, and diabetes history were not [22]. Symptoms of motor weakness, dysphagia, and dysarthria were associated with lesion-positive DWI, as was symptom duration >60 min [22]. Conversely, the rate of lesion-positive DWI was not significantly related to the presence of atrial fibrillation in a Japanese study of 464 patients [23]. Therefore, the significance of the lesion-positive DWI is unclear.

Here, we assessed the clinical characteristics, features, and outcomes of lesion-positive DWI in patients with TIA admitted to a stroke center.

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Materials and Methods

AThis was a retrospective study on a prospectively collected stroke database. We evaluated 235 patients with TIA who visited our stroke center between January 2009 and December 2015. Vascular neurologists made diagnoses in accordance with the WHO criteria, which define TIA as an acute loss of focal cerebral function lasting less than 24 h [4]. DWI was performed routinely in all patients with TIA upon admission (i.e., within 24 h of symptom onset) if the patient had no contraindications for magnetic resonance imaging (MRI). Lesion-positive DWI was defined as an increased signal on DWI with a reduced apparent diffusion coefficient.

Department of Neurology physicians recorded detailed baseline data for patients with TIA including demographics, clinical features, imaging features, and precise potential sources of cardioembolism, per the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification [24]. Modified Rankin scale (mRS) scores were acquired at admission and at discharge from the hospital [25]. All data collected were recorded prospectively in the medical center registry; the 3-month follow-up mRS score was determined via a telephone survey administered by a research nurse affiliated with the Department of Neurology [26]. For categorical variables, Pearson's chi-square test and Fisher's exact test were used to determine correlations with lesion-positive DWI. Association of lesion-positive DWI with cardioembolic risk stratification according to TOAST classification was calculated by excluding the effect of atrial fibrillation using the Cochran–Mantel–Haenszel test. Relative risk associated with each variable for lesion-positive DWI was calculated. For continuous variables, Student's t-test was used. Statistical analysis was performed using SPSS software.

Results

The proportion of patients with lesion-positive DWI was 14.0% among 235 subjects with TIA. Continuous etiological variables are presented in Table 1, and categorized variables are presented in Table 2. Only male sex, history of previous stroke, atrial fibrillation, and medium- to high-risk source of cardioembolism (TOAST classification) were found to be significantly associated with the presence of lesion-positive DWI. Atrial fibrillation showed the highest relative risk of cardioembolism. Medium- to high-risk sources of cardioembolism were not significantly related to lesion-positive DWI when the presence of atrial fibrillation was excluded ($p = 0.108$; Cochran–Mantel–Haenszel test). Although not significant, a trend toward association of sources of high-risk for cardioembolism (TOAST classification) with lesion-positive DWI was noted if atrial fibrillation was excluded ($p = 0.052$; Cochran–Mantel–Haenszel test). No association between the presence of lesion-positive DWI and clinical features was found (Table 3). Whether the patients had lesion-positive DWI was not related to an increase in mRS score during the hospital stay or at the 3-month follow-up after discharge (Table 4).

Discussion

We found that etiological factors associated with a high risk of stroke were also associated with the presence of lesion-positive DWI in patients with TIA. These factors included male sex, previous history of stroke, and presence of atrial fibrillation. A high risk of cardioembolism according to TOAST classification showed a trend toward association with lesion-positive DWI, but the relationship was not statistically significant when atrial fibrillation was excluded. No clinical features were associated with the presence of lesion-positive DWI. These findings differ from the previously reported large systematic review, which showed that traditional vascular risk factors (age, sex, diabetes, hypertension, and blood pressure) were not associated with lesion-positive DWI, while clinical features, such as motor weakness, dysarthria, aphasia, and time from onset > 60 min, were [22]. Although the association with the time from onset was not assessed in this study, the admission route and symptom onset during sleep or waking were assessed (Table 2). Patients admitted via the outpatient clinic and those with symptom onset noted during sleep likely underwent DWI longer after onset than did inpatients and those who first experienced symptoms while awake. However, no significant association was detected.

The differential findings may be due to differences in ethnicity, as well as differences in the medical environment. The hospital environment affected the time from onset to radiological assessment in an observational study [27]. Detection of ischemic lesions is difficult 1–12 h after TIA; therefore, different treatment and imaging protocols in different medical environments may affect detection of lesion-positive DWI in patients with TIA [28]. On the other hand, in a study of multi-modal MRI in patients with TIA, new lesions were found in 46.7% of patients who initially showed normal DWI findings at a follow-up a few days after onset [29]. Therefore, DWI findings in the acute TIA setting may not represent the presence of true tissue ischemia; variations in the time from onset and lack of DWI follow-up may be a limitation of current reports.

For prognosis, the mRS score was analyzed according to the presence of lesions on DWI, and no significant effect was noted. This is in accordance with a systematic review on outcomes of patients with non-disabling

Table 1. Continuous etiological variables in association to positive DWI

Characteristics (n)	DWI positive (n = 33)	DWI negative (n = 202)	*p*-value
Age - yr	63.42 ± 13.15 (33)	62.41 ± 13.56 (202)	0.688
Height - cm	162.93 ± 10.58 (32)	161.6 ± 9.33 (184)	0.465
Weight - kg	66.88 ± 11.21 (32)	64.53 ± 12.84 (184)	0.333
BMI	25.21 ± 3.65 (32)	24.56 ± 3.32 (184)	0.319
Smoking - PYrs	37 ± 10.59 (10)	31.94 ± 17.27 (41)	0.382

Values are presented as means ± S.D.
There were no significant differences between groups.
DWI, diffusion weighted image; n, numbers; BMI, body mass index; PYrs, pack years.

Table 2. Categorized etiological variables in association to positive DWI

Characteristics	DWI positive (n = 33)	DWI negative (n = 202)	*p*-value	RR (range)
Sex				
Male	23	99	0.038	1.42 (1.09–1.85)
Female	10	103		0.59 (0.35–1.01)
Admission route				
Outpatient	4	20	0.755	1.22 (0.45–3.36)
ER & in-hospital	29	182		0.98 (0.85–1.12)
Onset situation				
During sleep	3	24	1.000	0.83 (0.27–2.56)
During awake	21	136		1.03 (0.87–1.21)
Education				
≤ 9 years	12	65	1.000	0.99 (0.64–1.53)
> 9 years	12	64		1.01 (0.65–1.56)
Smoking				
Non-smoker	22	139	.686	0.95 (0.73–1.23)
Smoker	11	59		1.12 (0.66–1.9)
Previous TIA	3 (9.1%)	15 (7.4%)	0.727	1.21 (0.37–3.93)
Previous stroke	13 (39.4%)	38 (18.8%)	0.012	2.07 (1.25–3.44)
Previous CHD	4 (12.1%)	11 (5.4%)	0.238	2.23 (0.75–6.58)
Hypertension	19 (57.6%)	114 (56.4%)	0.850	1.04 (0.76–1.41)
Diabetes	8 (24.2%)	57 (28.2%)	0.833	0.86 (0.46–1.64)
Dyslipidemia	5 (15.2%)	25 (12.4%)	0.586	1.22 (0.5–2.95)
Atrial fibrillation	29 (87.9%)	15 (7.4%)	0.000	11.19 (6.77–18.49)
CE risk (+)	30 (90.9%)	26 (12.9%)	0.000	7.06 (4.86–10.27)

CE risk positive is defined as the patient with at least one medium-risk or high risk factors of cardioembolism according to TOAST classification.
DWI, diffusion weighted image; ER, emergency room; TIA, transient ischemic attack; CHD, coronary heart disease; CE, cardioembolism.

Table 3. Clinical features in association to positive DWI

Characteristics	DWI positive (n = 33, %)	DWI negative (n = 202, %)	*p*-value	RR (Range)
U/Ex weakness	19 (57.6)	116 (57.4)	1.000	1.00 (0.73–1.38)
L/Ex weakness	15 (45.5)	107 (53)	0.457	0.86 (0.58–1.27)
Numbness	2 (6.1)	23 (11.4)	0.544	0.53 (0.13–2.15)
Aphasia	2 (6.1)	6 (3)	0.312	2.04 (0.43–9.68)
Dysarthria	11 (33.3)	52 (25.7)	0.398	1.29 (0.76–2.21)
Dizziness	4 (12.1)	13 (6.4)	0.271	1.88 (0.65–5.43)
Facial palsy	1 (3)	3 (1.5)	0.456	2.04 (0.22–19.03)
Mental change	1 (3)	4 (2)	0.534	1.53 (0.18–13.27)
Ataxia	0 (0)	7 (3.5)	0.597	0.00 (0.00–0.00)
Imbalance	0 (0)	3 (1.5)	1.000	0.00 (0.00–0.00)
Visual disturbance	0 (0)	7 (3.5)	0.597	0.00 (0.00–0.00)
Vertigo	0 (0)	8 (4)	0.604	0.00 (0.00–0.00)

The numbers are shown along with percentage of the total patients for each group. DWI, diffusion weighted image; U/Ex, upper extremity; L/Ex, lower extremity; RR, relative risk.

Table 4. Prognosis in association to positive DWI

Characteristics	DWI positive (n = 33)	DWI negative (n = 202)	*p*-value
mRS, Admission (0/1/2/3/4)	5/8/2/0/0	37/39/26/4/1	0.511
mRS, Discharge (0/1/2/3)	12/2/1/0	65/26/3/3	0.534
mRS, 3 months (0/1/2)	6/3/0	23/6/4	0.395
ΔmRS, discharge - admission			
Increased	0	2	0.749
Not increased	15	95	
ΔmRS, 3 months - discharge			
Increased	3	10	0.579
Not increased	6	23	

ΔmRS, discharge - Admission indicates changes in mRS during hospital stay. ΔmRS, 3 months - discharge indicates changes in mRS 3 months after discharge. DWI, diffusion weighted image; mRS, modified rankin scale.

stroke, where the prognosis was similar between the DWI-negative and -positive groups [30], but contrary to previous reports where lesion-positive DWI was independently predictive of stroke recurrence [7–9].Several limitations of this study should be noted. First, this study was a retrospective analysis of patients with TIA. Second, this study had a small sample size, which limited the statistical power, and it was performed at a single center.

In conclusion, the etiological factors associated with lesion-positive DWI in patients with TIA were male sex, previous stroke history, and atrial fibrillation. Clinical features and prognosis were similar between lesion-pos-itive and negative groups. Future studies should include multi-center samples with large numbers, considering each unique medical environment. Routine acquisition of follow-up DWI for proper evaluation of the tissue-based definition of TIA should also be considered.

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