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DWI Lesion Patterns Predict Outcome in Stroke Patients with Thrombolysis

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Abstract

Background—Lesion patterns may predict prognosis after acute ischemic stroke within the middle cerebral artery (MCA) territory; yet it remains unclear whether such imaging prognostic factors are related to patient outcome after intravenous thrombolysis.

Aims—The aim of this study is to investigate the clinical outcome after intravenous thrombolysis in acute MCA ischemic strokes with respect to diffusion-weighted imaging (DWI) lesion patterns.

Methods—Consecutive acute ischemic stroke cases of the MCA territory treated over a 7-year period were retrospectively analyzed. All acute MCA stroke patients underwent a MRI scan before intravenous thrombolytic therapy was included. DWI lesions were divided into 6 patterns (territorial, other cortical, small superficial, internal border zone, small deep, and other deep infarcts). Lesion volumes were measured by dedicated imaging processing software. Favorable outcome was defined as modified Rankin scale (mRS) of 0–2 at 90 days.

Results—Among the 172 patients included in our study, 75 (43.6%) were observed to have territorial infarct patterns or other deep infarct patterns. These patients also had higher baseline NIHSS score ($p < 0.001$), a higher proportion of large cerebral artery occlusions ($p < 0.001$) and larger infarct volume ($p < 0.001$). Favorable outcome (mRS 0–2) was achieved in 89 patients (51.7%). After multivariable analysis, groups with specific lesion patterns, including territorial infarct and other deep infarct pattern, were independently associated with favorable outcome (OR 0.40; 95% CI 0.16–0.99; $p = 0.047$).

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Disclosure Statement

All authors have no conflict of interest.

Conclusions—Specific lesion patterns predict differential outcome after intravenous thrombolysis therapy in acute MCA stroke patients.

Keywords

Acute ischemic stroke; Thrombolysis; MRI; Clinical outcome

Introduction

Intravenous thrombolysis with tissue-type plasminogen activator (IV-tPA) is a well-proved treatment in ischemic stroke patients presenting within 4.5 h from symptoms onset [1, 2]. After thrombolytic therapy, recanalization is achieved only in 40% of middle cerebral artery (MCA) stroke patients [3] and half of these patients remain severely disabled or die [4]. Therefore, it is of great importance to identify the factors that predict clinical outcome after intravenous thrombolysis among acute MCA ischemic stroke patients [5]. Imaging-guided patient selection was successfully used in selecting patients for endovascular therapy. Several imaging factors [6] have been analyzed to determine whether they can predict outcome after intravenous thrombolysis in acute MCA stroke patients, including length of occlusion and distribution of occlusion. However, the definitions used for the MCA segments are variable in different studies and measure the length of occlusion can't be used in all centers. It is therefore important to develop a standard time and cost-effective imaging analysis method that can predict clinical outcome in these patients.

Being the most sensitive diagnostic modality in detecting acute ischemic lesions, diffusion-weighted imaging (DWI) can provide several important inputs for clinical analysis [7, 8]. Among them, DWI lesion pattern analysis is considered a simple and reasonable method to predict patients' clinical outcome. Previous studies [9, 10] have demonstrated that lesion patterns identified on DWI are correlated with the pathogenic mechanisms. The predictor role of lesion patterns to clinical outcome has also been proved in acute MCA ischemic stroke patients [5, 11]. However, little is known about whether MCA stroke patients treated with intravenous thrombolysis have different outcomes based on different lesion patterns.

In this study, we hypothesized that outcome after intravenous thrombolysis in patients with acute MCA ischemic stroke varies depending on lesion patterns. In particular, we investigated clinical and imaging predictors of poor response to systemic thrombolysis and evaluated whether patient outcome differs depending on infarct patterns.

Patients and Methods

Study Design

We performed a retrospective study on a cohort of patients diagnosed with an acute ischemic stroke and treated with IV-tPA. We reviewed all patients' imaging data from UCLA at the Neurovascular Imaging Research Core. In this analysis, we included only acute ischemic stroke patients with lesions involving MCA territory or border-zone areas. Clinical and imaging data were obtained from every patient with their informed consent and approval of the Ethic Committee. We excluded patients who (1) were <18 years old, (2) had infarcts in

multiple vascular territories beyond the unilateral MCA territory, (3) had no MRI results before intravenous thrombolysis, (4) had no MRA, CTA or conventional angiography results to determine the occlusion of carotid artery or MCA, (5) had lost follow-up data.

Data on clinical history, demographics, laboratory results, vascular risk factors were obtained as part of routine stroke care. Baseline stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) score. At the third-month follow-up, patients were interviewed in the outpatient clinic or through the telephone to evaluate clinical outcome in terms of the level of independence in performing the activities of daily living. Favorable outcome at 3 months was defined as modified Rankin scale (mRS) score 2.

Imaging Analysis

Emergency MRI was performed on a 3.0-T scanner. The MR protocol included DWI (single-shot echo-planar spin-echo sequence; 3 directions, $b = 1,000$), T2-weighted imaging and MR angiography. The topography of ischemic lesions was determined using published templates [12]. The MCA territory was divided into 3 subdivisions: deep territory, superficial anterior territory and superficial posterior territory. Patients were divided into 6 groups based on DWI patterns [13]. Territorial infarcts were infarcts involving 2 or more subdivisions. Other cortical infarcts were cortical infarcts involving one subdivision or cortical border zone. Small superficial infarcts were multiple small cortical infarcts (diameter <10 mm), or single or multiple superficial infarcts in the centrum ovale. Internal border zone infarcts were defined as multilocular chain-like lesions, confluent striated lesion patterns, or solitary lesions located in the supraventricular or paraventricular areas. Small deep infarcts were the small striato-capsular lesions involving striato-capsular area. Other deep infarcts were large striato-capsular lesions or concomitant DWI lesions outside the striato-capsular area. Lesion patterns were analyzed by two-stroke imaging experts (D.L. and F.S.), who were blinded to the clinical characteristics. Discrepancies were resolved by consensus.

In this study, we included only those patients with vascular results, including MRA, CTA or DSA, to determine the occlusion of cerebral vascular. Large cerebral artery occlusion was defined as internal carotid artery occlusion or M1 segment of MCA occlusion. One of the authors blinded to the clinical information analyzed the lesion volumes using a computer-assisted volumetric analysis program (Olea Medical, La Ciotat, France). DWI lesion volumes were quantified from the analysis of isotropic b1000 images and ADC maps with threshold $ADC < 600$. Lesions visible on DWI images were semi-automatically segmented using Osirix software. The final 3D volume was then computed using linear interpolation between slice and the slice spacing to obtain accurate estimates.

Statistical Analysis

Continuous variables with a normal distribution were described in terms of their mean and SD. Non-normally distributed variables were described as median and interquartile range (IQR). Continuous variables were compared with Mann–Whitney U test and categorical variables were compared using Pearson χ^2 or Fisher exact test, as appropriate. Logistic regression analyses were done to determine the independent predictors of favorable outcome

at 90 days (mRS 0–2). All covariates with a p value <0.1 in a univariate analysis were entered into this logistic regression model and a value of $p < 0.05$ was used to indicate statistical significance.

Results

Patients Characteristics at Baseline

During January 2007 and December 2013, a total of 172 patients met the inclusion criteria and were enrolled in this study. Baseline characteristics for the cohort are shown in table 1. The mean age was 67.0 ± 16.4 years with 44.8% being male patients. The median baseline NIHSS score was 13 (IQR 7–18) and onset to treatment time was 132.9 ± 48.7 min.

According to the different lesion patterns, patients with territorial infarcts (34/172, 19.8%) have a higher baseline NIHSS score (18.0 vs. 11.0, $p < 0.001$), a higher proportion of large cerebral artery occlusion (64.7 vs. 34.8%, $p = 0.001$) and a larger infarct volume (98.8 (73.3–146.9) vs. 14.3 (5.2–37.4), $p < 0.001$). Although territorial infarct patients were more likely to undergo an endovascular therapy (58.8 vs. 34.1%, $p = 0.008$), the percentage of patients with favorable outcome is significantly lower than others (32.4 vs. 56.5%, $p = 0.012$). Patients with small superficial infarcts (31/172, 18%) had a lower baseline NIHSS score ($p = 0.003$), reduced large cerebral artery occlusion ($p = 0.002$), smaller infarct volume ($p < 0.001$) and were less likely to undergo endovascular therapy ($p = 0.039$). Similarly to the small superficial infarct group, patients with other cortical infarct pattern also demonstrated a lower baseline NIHSS score (10.0 vs. 13.0, $p = 0.035$). In addition, endovascular therapy was less likely (21.6 vs. 43.7%, $p = 0.015$), large cerebral artery occlusion was less frequent (16.2 vs. 47.4%, $p = 0.001$), and infarct volume was larger (66.5 (32.1–86.6) vs. 16.2 (5.1–64.8), $p = 0.005$).

There was another deep infarct (41/172, 23.8%) that was the most popular lesion pattern in our study. The baseline NIHSS score of these patients was higher than others (15.0 vs. 11.0, $p = 0.001$) and more patients had large cerebral artery occlusions (65.9 vs. 32.8%, $p < 0.001$). In our analysis, more patients with other deep infarcts underwent endovascular therapy (56.1 vs. 33.6%, $p = 0.010$) and the onset to therapy time was shorter (117.1 ± 43.9 vs. 137.9 ± 49.3 , $p = 0.016$). As expected, the proportion of patients good outcome at 90 days (mRS ≤ 3) in this group was smaller than others (36.6 vs. 56.5%, $p = 0.026$).

Baseline Characteristics in Different Groups

Based on lesion pattern analysis results, the patients included in our study were divided into 2 different groups. Territorial infarct patients and other deep infarct patients were located in Group 1 (75/172, 43.6%), while the patients for the other 4 lesion patterns were located in Group 2. The characteristics of different groups are shown in table 2.

The history of hypertension is less frequent in Group 1 than Group 2 ($p = 0.045$). Other risk factors and baseline characteristics (including systolic blood pressure (SBP), blood glucose and cholesterol) were not significantly different in the 2 groups. The neurological symptoms of Group 1 were more severe than that of Group 2 ($p < 0.001$). As to imaging analysis, large cerebral artery occlusions were more frequent ($p < 0.001$) and infarct volumes were larger (p

< 0.001) in Group 1. The patients in Group 1 had a less favorable outcome (34.7 vs. 64.9%, $p < 0.001$) even though they were more likely to undergo an endovascular therapy ($p < 0.001$) and had a shorter onset-therapy time ($p = 0.008$).

Associative Factors of 90 Days Clinical Outcome

In our study, a favorable outcome (mRS 0–2) was observed in 89 patients (51.7%). Table 3 shows the potential predictors of clinical outcomes. The patients with a favorable outcome were significantly younger than those with a poor outcome ($p < 0.001$). The group with a favorable outcome also had a lower baseline NIHSS score ($p < 0.001$), lower proportion of large cerebral artery occlusion ($p = 0.004$), smaller infarct volume ($p = 0.029$) and less territorial infarct or other deep infarct ($p < 0.001$). After univariate analysis, the percent of endovascular therapy ($p = 0.076$) were included in multivariate logistic regression. The result of multivariate logistic regression is shown in table 3. After adjustment for confounding factors, special lesion patterns, including territorial infarct patterns and other deep infarct patterns, were independently associated with a favorable outcome (OR 0.40; 95% CI 0.16–0.99; $p = 0.047$).

Discussion

The results of our study demonstrated that patients with territorial infarct pattern or other deep infarct pattern were more likely to have larger lesion volume, more cerebral artery occlusion, higher chance of undergoing an endovascular therapy and shorter onset to therapy time, in acute MCA stroke patients with intravenous thrombolysis. The presence of these specific lesion patterns was independently associated with poor outcome after IV-tPA in these patients.

Three thrombectomy clinical trials published in 2013, IMS III [14], MR RESCUE [15] and SYNTHESIS [16], reported neutral results on clinical outcome. However, the results from recent clinical trials [17–19] provided good evidence for early thrombectomy with stent retrievers. The use of imaging criteria to select patients might be one of the most important explanations for that difference. In ESCAPE trials [18], only patients with a CTA-confirmed occlusion of the carotid T or the MCA, good collaterals on multiphase CTA, and a CT-ASPECTS >5 were included. The MR CLEAN trial subgroup analysis [17] also showed the benefit of thrombectomy for patients with ASPECT scores ≥ 5 points but probably not with ASPECT scores between 0 and 4. Therefore, it is well accepted that infarct volume is an important criterion needed to select patients for endovascular therapy. A previous study [20] has found that patients with large deep white matter lesion on DWI were poor candidates for endovascular therapy. In this study, patients with territorial infarct or other deep infarct patterns had larger infarct volume than others. Although more endovascular therapies were performed, their clinical outcome was still worse than others, and the independent association of endovascular therapy with clinical outcome was not tested. Then, our result is in agreement with the consensus that large infarct is unsuitable for thrombectomy.

DWI infarct volume has also been proved to predict short-term recovery in patients with MCA occlusion who underwent intravenous thrombolysis [21] or endovascular therapy [22]. However, another study [6] found that cerebral blood volume ASPECTS score is not the

independent predictor of clinical outcome after intravenous thrombolysis in MCA ischemic stroke patients. In our study, infarct volume was also not the independent predictor of patients' clinical outcome. We assumed that the progression of DWI infarct volume accounted for the controversy. DWI-PWI (perfusion-weighted imaging) mismatch presents in some patients, and lesions on early DWI may result in a significant increase on follow-up image [7, 23]. A previous study [24] has demonstrated that the degree of increase in DWI volume differed depending on the DWI lesion pattern, and small DWI lesion volume could have poorer prognosis in special lesion pattern. Therefore, lesion patterns can play a powerful predictor role by combination of baseline lesion volume and progression of lesion volume.

In a rodent model for ischemic stroke, different ADC patterns were related to different functional outcomes in lesions of similar size after permanent MCA occlusion [25]. For clinical patients, DWI lesion pattern analysis is also considered a simple and reasonable method to predict patient outcome [13]. In addition to this, likely mechanisms of stroke can be explored through lesion pattern analysis and the recurrence of stroke varied according to different lesion patterns [10]. Also, lesion pattern analysis is feasible for clinical practice because it is less time consuming and more reliable for neurologist. Bang et al. [13] found that DWI lesion patterns predict prognosis after acute ischemic stroke within the MCA territory. Another study [26] also demonstrated that specific lesion patterns were related to cerebral arterial occlusion mechanisms and were correlated with functional outcome. Lesion patterns on DWI might be a clue for determining ischemic stroke etiology on patients with MCA occlusion. Similar to these studies, our study has proved that DWI lesion patterns independently predicted the clinical outcome of acute MCA ischemic stroke patients after IV-tPA treatment.

There are some limitations to our study. First, this study is a single-center, retrospective study. The number of patients is comparatively smaller for complex analyses. Our results remain to be confirmed in larger multicenter trials. Accordingly, the lesion patterns were analyzed by stroke imaging experts. To reduce inter-reader variability and to enable the systematic analysis of a large dataset, there is an overt need for an automatic tool that would be able to classify lesions accurately in the blink of an eye.

In conclusion, we found that lesion patterns were independent predictors of clinical outcome in patients with acute MCA stroke after intravenous thrombolysis. Because the pathophysiologic mechanisms of ischemic stroke vary in different lesion patterns, more aggressive endovascular reperfusion treatment should be considered according to special lesion patterns. Future clinical trials on mechanical thrombectomy could include lesion patterns as one of the patient selection criteria.

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Table 1

Patient characteristics grouped by lesion patterns

	A – territorial infarcts (n = 34)	B – small superficial infarcts (n = 31)	C – other cortical infarcts (n = 37)	D – internal border zone infarcts (n = 10)	E – small deep infarcts (n = 19)	F – other deep infarcts (n = 41)
Age, mean ± SD	62.6±16.9	67.8±15.0	65.6±16.7	72.1±17.1	67.5±15.9	69.7±16.7
Male, n (%)	15 (44.1)	18 (58.1)	16 (43.2)	4 (40.0)	7 (36.8)	17 (41.5)
Risk factors, n (%)						
Hypertension	20 (58.8)	21 (67.7)	28 (75.7)	8 (80.0)	14 (73.7)	24 (58.5)
Diabetes	7 (20.6)	7 (22.6)	3 (8.1)	3 (30.0)	3 (15.8)	9 (22.0)
Hyperlipidemia	14 (41.2)	14 (45.2)	20 (54.1)	3 (30.0)	9 (47.4)	21 (51.2)
Ever smoker	5 (14.7)	1 (3.2)	5 (13.5)	2 (20.0)	1 (5.3)	5 (12.2)
Previous stroke/TIA	7 (20.6)	7 (22.6)	9 (24.3)	4 (40.0)	5 (26.3)	6 (14.6)
CAD	5 (14.7)	0 (0) *	6 (16.2)	1 (10.0)	2 (10.5)	4 (9.8)
Heart failure	3 (8.8)	1 (3.2)	6 (16.2) *	1 (10.0)	0 (0)	3 (7.3)
AF	10 (29.4)	10 (32.3)	11 (29.7)	5 (50.0)	2 (10.5)	8 (19.5)
Baseline NIHSS score, median (IQR)	18.0 (14.0–21.0) *	8.0 (4.0–15.0) *	10.0 (4.5–15.5) *	8.5 (4.5–15.0)	7.0 (5.0–10.0) *	15.0 (12.0–21.0) *
SBP, mm Hg, median (IQR)	152.0±26.7	143.2±28.7 *	155.0±23.3	165.1±37.2	152.3±32.7	160.5±27.4
Blood glucose, mg/dl, median (IQR)	132.0±31.8	125.0±37.0	118.9±24.3 *	145.1±43.6	123.5±25.7	134.3±42.5
Cholesterol	164.8±39.1	157.0±47.8	167.3±44.2	174.7±42.0	170.8±43.1	161.2±37.7
Onset to therapy time	127.7±44.9	134.2±47.5	146.3±49.3	139.3±67.9	145.1±49.9	117.1±43.9 *
Need more therapy, n (%)	20 (58.8) *	7 (22.6) *	8 (21.6) *	3 (30.0)	6 (31.6)	23 (56.1) *
Large cerebral artery occlusion	22 (64.7) *	5 (16.1) *	6 (16.2) *	5 (50.0)	5 (26.3)	27 (65.9) *
Infarction volume on DWI	98.8 (73.3–146.9)	5.2 (3.7–7.4) *	66.5 (32.1–86.6) *	15.5 (13.0–20.7)	3.0 (2.8–3.1) *	19.6 (14.8–46.7)
90 days mRS 2	11 (32.4) *	19 (61.3)	24 (64.9)	7 (70.0)	13 (68.4)	15 (36.6) *

TIA = Transient ischemic attack; CAD = coronary artery disease; AF = atrial fibrillation.

*
p < 0.05.

Table 2

Patient characteristics grouped by the lesion pattern subset

Characteristics	Group 1 (n = 75) Infarction pattern – A + F	Group 2 (n = 97) Infarction pattern – B + C + D + E	p value
Age, mean ± SD	66.5±17.1	67.3±15.9	0.734
Male, n (%)	32 (42.7)	45 (46.4)	0.626
Risk factors, n (%)			
Hypertension	44 (58.7)	71 (73.2)	0.045 *
Diabetes	16 (21.3)	16 (16.5)	0.419
Hyperlipidemia	35 (46.7)	46 (47.4)	0.922
Ever smoker	10 (13.3)	9 (9.3)	0.400
Previous stroke/TIA	13 (17.3)	25 (25.8)	0.186
CAD	9 (12.0)	9 (9.3)	0.563
Heart failure	6 (8.0)	8 (8.2)	0.953
AF	18 (24.0)	28 (28.9)	0.475
Baseline NIHSS score, median (IQR)	17.0 (13.0–21.0)	8.0 (5.0–15.0)	<0.001 *
SBP, mm Hg, median (IQR)	156.7±27.3	151.8±28.9	0.260
Blood glucose, mg/dl, median (IQR)	133.3±37.8	124.5±31.8	0.099
Cholesterol	162.8±38.1	165.5±44.7	0.680
Onset to therapy time	121.9±44.4	141.5±50.5	0.008 *
Need more therapy, n (%)	43 (57.3)	24 (24.7)	<0.001 *
Large cerebral artery occlusion	49 (65.3)	21 (21.6)	<0.001 *
Infarction volume on DWI	55.3 (19.3–91.0)	8.6 (3.3–28.2)	<0.001 *
90 days mRS 2	26 (34.7)	63 (64.9)	<0.001 *

TIA = Transient ischemic attack; CAD = coronary artery disease; AF = atrial fibrillation.

* p < 0.05.

Table 3

Patient characteristics grouped by 90 days outcomes

Characteristics	Patients with favorable outcome mRS <3 (n = 89)	Patients with poor outcome mRS ≥ 3 (n = 83)	p value	OR	95% CI	p value
Age, mean ± SD	61.8±15.4	72.5±15.7	<0.001*	0.96	0.94–0.98	<0.001*
Male, n (%)	44 (49.4)	33 (39.8)	0.202			
Risk factors, n (%)						
Hypertension	55 (61.8)	60 (72.3)	0.144			
Diabetes	15 (16.9)	17 (20.5)	0.541			
Hyperlipidemia	42 (47.2)	39 (47.0)	0.979			
Ever smoker	8 (9.0)	11 (13.3)	0.373			
Previous stroke/TIA	16 (18.0)	22 (26.5)	0.178			
CAD	11 (12.4)	7 (8.4)	0.401			
Heart failure	7 (7.9)	7 (8.4)	0.892			
AF	21 (23.6)	25 (30.1)	0.334			
Baseline NIHSS score, median (IQR)	9.0 (4.0–15.5)	16.0 (11.0–20.0)	<0.001*	0.95	0.89–1.00	0.045*
SBP, mm Hg, median (IQR)	150.6±26.7	157.4±29.5	0.115			
Blood glucose, mg/dl, median (IQR)	125.6±34.2	131.3±35.2	0.284			
Cholesterol	168.1±43.8	160.2±39.6	0.219			
Onset to therapy time	135.2±54.3	130.5±42.2	0.521			
Need more therapy, n (%)	29 (32.6)	38 (45.8)	0.076*	1.08	0.52–2.27	0.836
Large cerebral artery occlusion	27 (30.3)	43 (51.8)	0.004*	1.37	0.64–2.97	0.421
Infarction volume on DWI	17.1 (5.0–46.2)	35.3 (8.3–73.2)	0.029*	1.00	0.99–1.01	0.998
Patients in infarction pattern group 1 (infarction pattern A + F)	26 (29.2)	49 (59.0)	<0.001*	0.40	0.16–0.99	0.047*

TIA = Transient ischemic attack; CAD = coronary artery disease; AF = atrial fibrillation.