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Original Article

Analysis of DWI ASPECTS and Recanalization Outcomes of Patients with Acute-phase Cerebral Infarction

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In order to rapidly judge the response to intravenous tissue plasminogen activator (Ⅳ tPA) treatment, we retrospectively analyzed clinical data, such as MRI diffusion-weighted images (DWI), and treatment outcomes in 73 patients who developed anterior circulation disorders. The patients with favorable outcomes (modified Rankin Scale [mRS]: 2 or less) at discharge accounted for 32.9%. In these patients, the National Institutes of Health Stroke Scale (NIHSS) value, DWI Alberta Stroke Programme Early CT Score (ASPECTS), and the incidence of large artery (internal carotid artery [ICA]/ sphenoidal segment of the middle cerebral artery [M1]) occlusion at their hospital visit were lower, higher, and lower, respectively (all $P < 0.05$ in univariate analysis). Multivariate analysis showed significant differences in DWI ASPECTS and the incidence of large artery occlusion. A DWI ASPECTS of at least 8 was found to be predictive of favorable outcomes. However, subclass analysis in the group with a DWI ASPECTS of 8 or higher predicting favorable outcome revealed 13 patients (41.9%) with unfavorable (mRS, 3-6) outcome. The factor associated with unfavorable outcomes is ICA occlusion. The combination of DWI ASPECTS and MRA appeared to be useful for predicting outcomes of Ⅳ tPA.

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Introduction

Treatment outcomes of acute cerebrovascular occlusion have improved greatly with the aid of intravenous tissue plasminogen activator (Ⅳ tPA) treatment.[1,2] However, Ⅳ tPA treatment is not effective in some cases, for example in patients with large artery occlusions.[3] It was recently reported that mechanical recanalization is effective in rescuing patients with large artery occlusions.[4,5] Additional recanalization has been considered, for example in order to extend the therapeutic time window before the treatment. A common magnetic resonance imaging (MRI) profile in patients with acute cerebrovascular occlusion is an area of perfusion deficit on perfusion weighted images (PWI) that is larger than the lesion on diffusion-weighted images (DWI) that may partly reflect irreversibly damaged brain tissue. It is reported that MRI evidence of this DWI-PWI mismatch is useful for expanding the indications for recanalization.[6-9] However, it is impossible to prepare and examine PWI for all patients receiving time-constrained acute phase treatments in the clinical practice. In the clinical setting, the indication for recanalization is considered when the patient has the discrepancy between the small lesion on DWI and severe clinical symptom (DWI-clinical mismatch). The usefulness of DWI Alberta Stroke Programme Early CT Score (ASPECTS, Figure 1) as a quantitative evaluation tool has been noted.[10,11] The DWI ASPECTS is a quantitative score, which represents non-ischemic areas of the middle cerebral artery territory that is divided into 11 regions. In this study, we analyzed

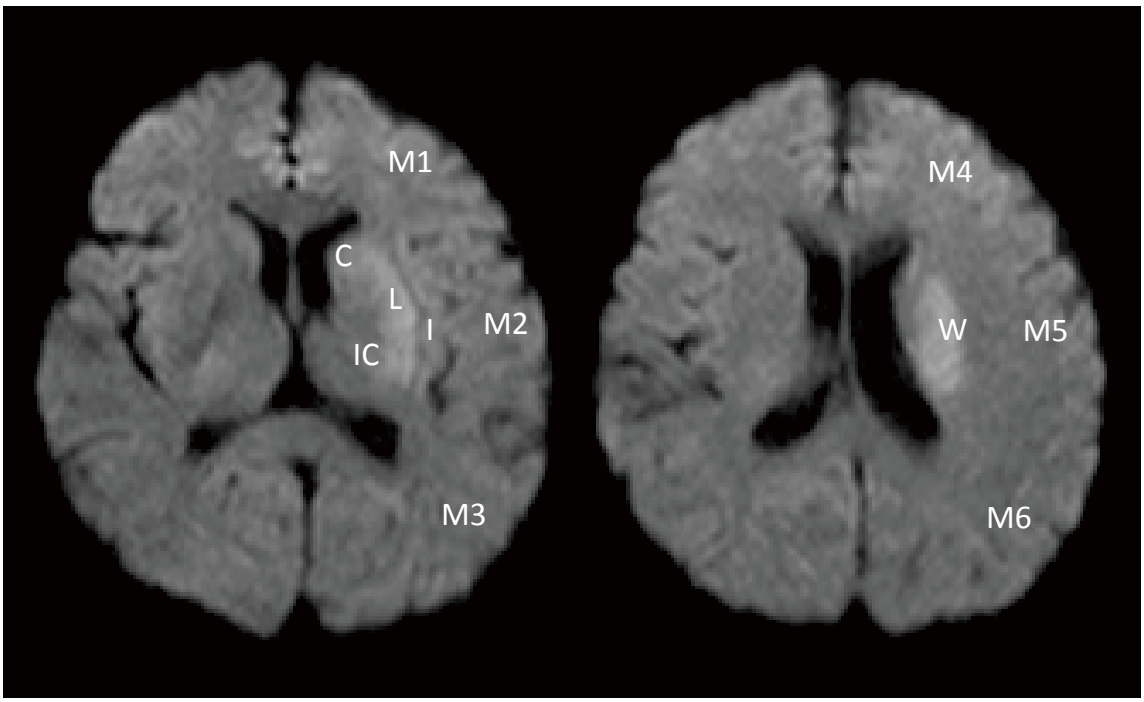

Figure 1 : DWI ASPECTS is evaluated in 11 regions: 10 ASPECTS (Alberta stroke programme early CT score) sites and a white matter (W) lesion. If abnormal signals due to infarction are detected, the count is 0; if they are not detected, the count is 1. If no infarctions are ultimately observed, the total score is 11; if infarction is observed in all target regions, the total score is 0. C: caudate,; L: lentiform,; IC: internal capsule,; I: insular ribbon,; M1: anterior middle cerebral artery (MCA) cortex,; M2: MCA cortex lateral to the insular ribbon,; M3: posterior MCA cortex,; M4, M5, and M6 are anterior, lateral, and posterior MCA territories, respectively, immediately superior to M1, M2, and M3, respectively, rostral to basal ganglia,; W: white matter (corona radiate).

clinical data, including DWI ASPECTS and treatment outcomes, in patients receiving Ⅳ tPA to promptly assess response to Ⅳ tPA and identify patients with no response to Ⅳ tPA who require intravascular surgery.

Patients and Methods

We reviewed 101 consecutive patients, who received Ⅳ tPA for their acute-phase cerebral infarction at the National Hospital Organization Disaster Medical Center in a period between November 2005 and February 2011. The Ⅳ tPA treatment was performed in accordance with the therapeutic guidelines[12] of the Japan Alteplase Clinical Trial (J-ACT). Of these 101 patients, 73 were selected for this study because they were judged to have an anterior circulation disorder by MRI before Ⅳ tPA treatment was performed. MRI studies, including DWI, T2*, and MR angiography (MRA) were performed to identify occluded arteries. The MRI was performed with a 1.5T MR imager (Intera Release 8; Philips Medical Systems, Best, the Netherlands). DWI ASPECTS was used to evaluate the affected middle cerebral artery territory. The presence of cerebral artery occlusion was assessed using MRA. Occluded arteries on initial MRA were classified as internal cerebral artery (ICA) occlusion, sphenoidal segment of the middle cerebral artery (MCA) (M1) occlusion, occlusion distal to the insular segment of MCA (M2), and perforator occlusion. The National Institutes of Health Stroke Scale (NIHSS) was applied for assessments prior to treatment. Cerebral infarction was classified into 5 types according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[13]: cardiogenic embolism, atherothrombotic embolism, lacunar infarction, unclassifiable cerebral infarction, and other cerebral infarction. The presence or absence of intracranial hemorrhage was examined by computed tomography (CT) or MRI T2* within 36 h of initiating Ⅳ tPA treatment. Hemorrhage with NIHSS of 1 or higher was defined as symptomatic intracranial hemorrhage. The modified Rankin Scale (mRS) was determined at discharge. Results are given as mean ± SD. To

extract factors that predict favorable outcomes (mRS, 0-2), statistical analysis was performed using PASW® statistics 18 (SPSS Inc, Chicago, IL). The significance of intergroup differences was assessed using the χ^2 test or Fisher's exact test for categorical variables (sex, occluded artery, occluded side), and Student's *t* test for parametric variables (age, NIHSS value, DWI ASPECTS, time from symptom onset to treatment). Multivariate logistic regression analysis was performed to determine factors that could be considered to be independent predictors of favorable outcome after tPA thrombolysis. Values of $P < 0.05$ were considered statistically significant. Spearman's rank correlation coefficients were used to test the association between the baseline DWI ASPECTS and mRS at discharge. The threshold DWI ASPECTS predicting favorable outcomes was determined from the receiver operating characteristic (ROC) curve. Subclass analysis was performed in the group predicted to have favorable outcomes. Factors associated with symptomatic intracranial hemorrhage were analyzed. The present study was approved by the ethics committees of Tokyo Medical and Dental University and the National Hospital Organization Disaster Medical Center.

Results

Of the 73 patients, 48 (65.8%) were men. Mean age was 71.6 ± 9.0 years. Clinical disease types were cardiogenic in 58 (79.5%) cases, atherothrombotic in 8 (11.0%), and lacunar infarction in 5 (6.8%). The pre-administration NIHSS value was 15.0 ± 6.9. The culprit vessels were the ICA in 16 (21.9%) cases and the MCA in 56 (76.7%). The occluded segments of the MCA were M1 in 35 (47.9%) cases, the distal side of M2 in 16 (21.9%), and the perforator of the MCA in 5 (6.8%). The mean DWI ASPECTS was 6.7 ± 2.7 (Table 1).

There were 14 cases (19.2%) with intracranial hemorrhage within 36 hours of administration; among them, 4 (5.5%) were symptomatic. There were no deaths due to intracranial hemorrhage (Table 2).

Twenty-four (32.9%) of 73 patients had favorable outcomes (mRS, 0-2) at discharge. In those patients, NIHSS value, DWI ASPECTS, and the incidence of large artery (ICA/M1) occlusion at their hospital visit were lower, higher, and lower than in patients with unfavorable outcomes (mRS, 3-6), respectively (all $P < 0.05$ in univariate analysis). Factors showing a significant difference on univariate analysis were subjected to multivariate analysis, which showed significant differences in DWI ASPECTS and the incidence of large artery occlusion (Table 3).

Table 1. Patient characteristics.

		n=73	(%)
sex	Male	48	65.8
	Female	25	34.2
age	<20	0	0.0
	20 to <65	16	21.9
	≥65 to <75	28	38.4
	≥75	29	39.7
	Mean ± SD	71.6 ± 9.0	
Clinical disease type	Cardiogenic embolism	58	79.5
	Atherothrombotic infarction	8	11.0
	Lacunar infarction	5	6.8
	Unknown/Not described	2	2.7
Pre-treatment NIHSS	≤4	3	4.1
	5 to 9	15	20.5
	10 to 14	16	21.9
	15 to 20	22	30.1
	≥21	17	23.3
	Of the above, ≥23	11	15.1
	Mean ± SD	15.0 ± 6.9	
Occluded vessel	ICA	16	21.9
	MCA	56	76.7
	M1	35	47.9
	Distal to M2	16	21.9
	MCA perforator	5	6.8
	Unknown	1	1.4
DWI ASPECTS	Mean ± SD	6.7 ± 2.7	

Table 2. Onset and frequency of hemorrhagic adverse drug reactions (ADR).

	n=73	(%)
Onset of ADR		
Onset of intracranial hemorrhage (within 36 hours)	14	19.2
Onset of symptomatic intracranial hemorrhage (within 36 hours)	4	5.5
Death due to intracranial hemorrhage	0	0.0
Death from all causes	8	11.0

The pre-administration DWI ASPECTS and mRS at discharge showed a negative correlation (Spearman correlation coefficient = -0.53, $P < 0.01$); i.e., the higher the DWI ASPECTS, the better were the outcomes (Figure 2).

From the results of the ROC analysis as a means of identification of the optimal cutoff point[14,15], the cutoff DWI ASPECTS predicting favorable outcomes (mRS, 0-2) was estimated to be 8 (sensitivity, 75.0%; specificity,

Table 3. Factors contributing to favorable outcomes.

	mRS ≤ 2 (n=24)	mRS ≥ 3 (n=49)	P*1	OR (95%CI)	P*2
age*3	69.0 ± 8.9	72.8 ± 8.9	0.094		
Male, n (%)	16 (66.7)	32 (65.3)	0.908		
NIHSS*3	11.0 ± 6.1	17.0 ± 6.4	<0.001	0.92 (0.82-1.02)	0.124
DWI ASPECTS*3	8.4 ± 1.7	5.9 ± 2.7	<0.001	1.38 (1.02-1.88)	0.039
Occluded artery					
Large artery (ICA/M1), n (%)	10 (41.7)	41 (83.7)	< 0.001	0.23 (0.07-0.78)	0.018
ICA, n (%)	1 (4.2)	15 (30.6)	0.014		
M1, n (%)	9 (37.5)	26 (53.1)	0.226		
Distal to M2 or perforator, n (%)	14 (58.3)	8 (16.3)	<0.001		
Occlusion of the left side, n (%)	9 (37.5)	28 (57.1)	0.115		
Time from symptom onset to treatment, minutes*3	136.6 ± 27.0	138.3 ± 29.0	0.806		

*1 *P* values from the χ^2 test, Fisher's exact test, Student's *t* test, or Mann–Whitney *U* test

*2 Multivariate logistic regression analysis was performed for NIHSS, DWI ASPECTS and the incidence of large artery occlusion.

*3 mean ± SD

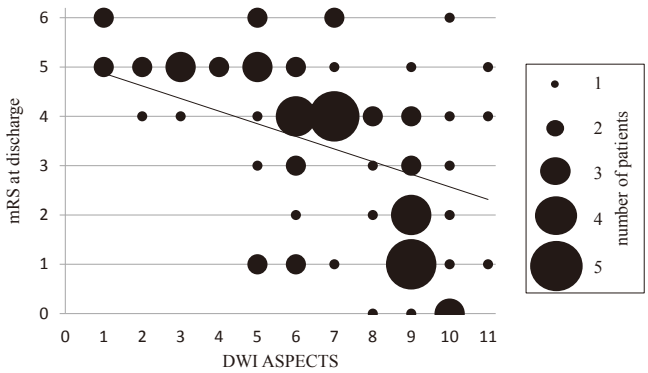

Figure 2 : Relationship between DWI ASPECTS and mRS at discharge.

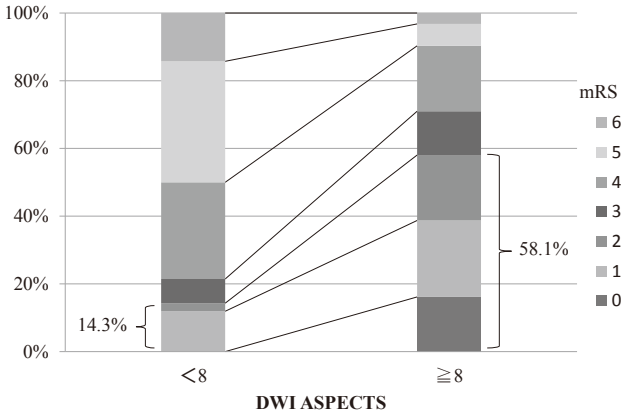

Figure 4 : mRS at discharge of patients with a DWI ASPECTS of 8 or higher/less than 8.

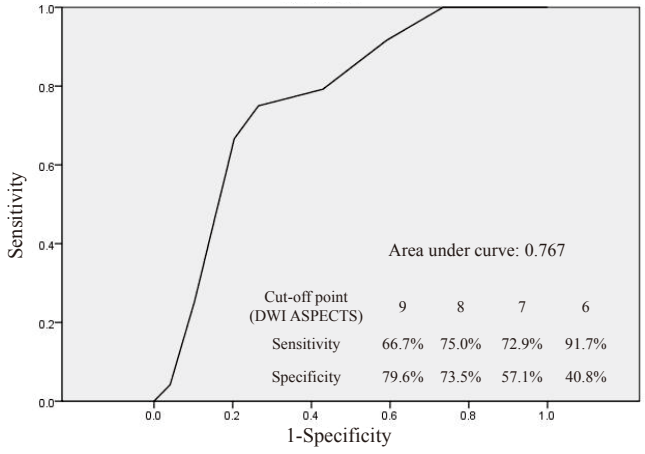

Figure 3 : Receiver operating characteristic curves for the ability of the DWI ASPECTS to predict favorable outcome (mRS 0-2).

73.5%; area under the curve [AUC], 0.767; Figure 3). A higher DWI ASPECTS, i.e., 8 and above, favored a better outcome. Eighteen (58.1%) of 31 patients with a DWI ASPECTS of 8 or higher and 6 (14.3%) of 42 patients with a DWI ASPECTS of 7 or lower had favorable outcomes (mRS, 0-2) at discharge; the former rate was significantly ($P < 0.01$) higher than the latter (Figure 4).

Subclass analysis in the group with a DWI ASPECTS of 8 or higher revealed 13 patients with unfavorable (mRS, 3-6) outcome. The factor associated with unfavorable outcomes is ICA occlusion (Table 4). In these 13 patients with unfavorable outcomes, the occluded artery was the ICA in 3 patients, M1 in 5, and the distal side of M2 in 5. Unfavorable outcomes in 3 patients with ICA occlusion were attributed to extensive

Table 4. Factors contributing to poor outcomes in patients with a DWI ASPECTS of 8 or higher.

	mRS ≤ 2 (n=18)	mRS ≥ 3 (n=13)	P*1
age*2	71.1 ± 6.1	70.9 ± 8.6	0.960
Male, n (%)	13 (72.2)	7 (53.8)	0.291
NIHSS*2	10.0 ± 5.0	13.4 ± 6.3	0.105
DWI ASPECTS*2	9.3 ± 0.8	9.3 ± 1.0	0.926
Occluded artery			
Large artery (ICA/M1), n (%)	8 (44.4)	8 (61.5)	0.347
ICA, n (%)	0 (0)	3 (23.1)	0.032
M1, n (%)	8 (44.4)	5 (38.5)	0.739
Distal to M2 or perforator, n (%)	10 (55.6)	5 (38.5)	0.347
Occlusion of the left side, n (%)	8 (44.4)	9 (69.2)	0.275
Time from symptom onset to treatment, minutes*2	132.8 ± 28.4	135.7 ± 38.7	0.810

*1 *P* values from the χ^2 test, Fisher's exact test, Student's *t* test and Mann–Whitney *U* test

*2 mean ± SD

cerebral infarction due to failure of recanalization of the ICA. In the other 10 patients, infarction localized in the inner capsule, white matter (corona radiata), language area, and motor cortex, as assessed by the DWI ASPECTS, caused physical impediments such as hemiplegia and aphasia, resulting in unfavorable outcomes.

Symptomatic intracranial hemorrhage occurred in 4 (12.1%) of 33 patients with DWI ASPECTS of 6 or less. This incidence rate was significantly higher than that in 40 patients with DWI ASPECTS of 7 or higher, 0% (P = 0.038, Figure 5). Thus, the cutoff DWI ASPECTS predicting symptomatic intracranial hemorrhage was set to be 6 (sensitivity, 100%; specificity, 58.0%). According to the univariate analysis, the factors associated with symptomatic intracranial hemorrhage within 36 h after Ⅳ tPA treatment were M1 occlusion and low DWI ASPECTS (Table 5). In all patients who had experienced symptomatic intracranial hemorrhage, DWI ASPECTS was 6 or less, and the mean was 4.0 ± 2.2, significantly (p = 0.036) lower than that in patients who had not experienced symptomatic hemorrhage, 6.9 ± 2.7. Multivariate analysis revealed no associated factors.

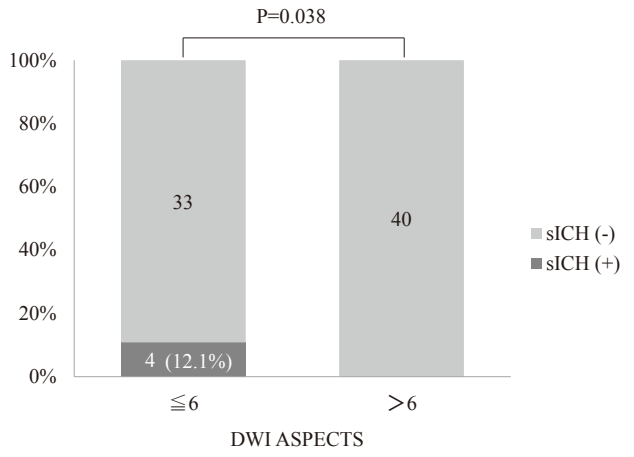

Figure 5 : Incidence of sICH in patients with a DWI ASPECTS of 6 or lower/ more than 6.

Discussion

Among patients with acute cerebrovascular occlusion who had been treated with Ⅳ tPA, those with anterior circulation occlusion in whom the DWI ASPECTS had been evaluated by pre-treatment MRI/A were examined for their clinical disease types, as well as outcomes and complications. Relationships between the DWI ASPECTS and outcome have been reported, and the optimal cut-off DWI ASPECTS for predicting outcomes has been discussed from various aspects.[15,16] Our study also showed that there were more patients with favorable outcomes when the pre-treatment DWI ASPECTS was 8 or higher (Figure 3). Despite slight differences in cut-off points, our study was consistent with previous studies, indicating that the higher the DWI ASPECTS, the better the outcome is predicted to be.

We conducted detailed examination to find causes of unfavorable outcomes in patients with DWI ASPECTS of 8 or higher predicting favorable outcomes. In 3 of these patients, the occlusion was located in the ICA and unfavorable outcomes (Table 4) were attributed to extensive cerebral infarction

Table 5. Factors contributing to symptomatic intracranial hemorrhage (sICH).

	sICH (n=4)	no sICH (n=69)	P*1
age*2	77.3 ± 4.6	71.3 ± 9.1	0.199
Male, n (%)	3 (75.0)	45 (65.2)	0.689
NIHSS*2	18.3 ± 5.9	14.8 ± 6.9	0.338
DWI ASPECTS*2	4.0 ± 2.2	6.9 ± 2.7	0.036
Occluded artery			
Large artery (ICA/M1), n (%)	4 (100)	47 (68.1)	0.177
ICA, n (%)	0 (0)	16 (23.2)	0.276
M1, n (%)	4 (100)	31 (44.9)	0.032
Distal to M2 or perforator, n (%)	0 (0)	22 (31.9)	0.177
Occlusion of the left side, n (%)	3 (75)	33 (47.8)	0.291

*1 *P* values from the χ^2 test, Student's *t* test and Mann–Whitney *U* test

*2 mean ± SD

due to no recanalization after Ⅳ tPA treatment. A high DWI ASPECTS despite the presence of an ICA occlusion means that the collateral flow is maintained. If occluded blood vessels are recanalized, infarction can be avoided, such that favorable outcomes can be expected. However, it is known that recanalization with Ⅳ tPA may not be expected in cases with large artery occlusions.[3] Patients with large artery occlusion, even if their DWI ASPECTS is 8 or higher, can still have poor outcomes because Ⅳ tPA treatment alone cannot assure recanalization. On the other hand, mechanical recanalization after Ⅳ tPA treatment reportedly increases the rate of recanalization.[17] In patients with a high DWI ASPECTS who have an ICA occlusion, outcomes may be improved by mechanical recanalization following Ⅳ tPA treatment. Meanwhile, in 10 patients, ischemic changes assessed by DWI ASPECTS were found in eloquent areas such as the inner capsule, corona radiata, and language area. It was confirmed that even in patients with DWI ASPECTS of 8 or higher, ischemia in the eloquent areas did not result in favorable outcomes regardless of the location of artery occlusion. In these cases, the DWI-clinical mismatch would not serve as the basis of clinical indications for further revascularization. Our extensive search of the literature indicated that there were no studies reporting on analysis of the causes for unfavorable outcomes by detailed examination of patients whose outcomes after Ⅳ tPA treatment were predicted to be favorable but turned out to be unfavorable.

Symptomatic intracranial hemorrhage was found to have developed in the group with a DWI ASPECTS of 6 or less (Table 5 and Figure 5). Low DWI ASPECTS indicates irreversible, diffuse cerebral ischemia, suggesting that reperfusion injury may cause bleeding. Thus, attention should be paid to hemorrhagic complications, when additional recanalization is selected for patients with a DWI ASPECTS of 6 or less.

There are cases in which satisfactory recovery is attained when motor and language areas are preserved by recanalization of one of the occluded arteries of the peripheral MCA region following examination of DWI-PWI mismatch of each penumbra. Such extensive exploration would improve individual outcome. On the other hand, it is also true that, in a case in the acute phase cerebral infarction, there is not enough time for careful study. Therefore, we need a simple index for identifying DWI-clinical mismatch. This study revealed that owing to an ICA occlusion, some patients had not shown satisfactory improvement of the outcomes, despite having a DWI ASPECTS of 8 or higher, which predicts favorable outcomes. Such patients may require additional revascularization, including mechanical recanalization. Results from combining the DWI ASPECTS and MRA can be obtained more quickly than results from perfusion analysis, and thus, may be useful as a simple quantitative index for DWI clinical mismatch, when additional recanalization following Ⅳ tPA treatment is considered.

Conclusion

We found that treatment of patients with acute cerebrovascular occlusion showing a pre-treatment DWI ASPECTS of 8 or higher with Ⅳ tPA resulted in favorable outcomes at discharge. However, with a disease type such as ICA occlusion, outcomes were often unfavorable even when the DWI ASPECTS was 8 or higher. In addition, symptomatic hemorrhagic complications were observed in considerable patients with a DWI ASPECTS of 6 or lower. In the National

Hospital Organization Disaster Medical Center, we are currently performing mechanical recanalization in patients with ICA occlusions showing a DWI ASPECTS of 8 or higher and in whom Ⅳ-tPA treatment was ineffective. We must wait for further studies to ascertain whether this treatment method actually improves the outcomes of these patients.

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