Predictors for Hemorrhagic Transformation with Intravenous Tissue Plasminogen Activator in Acute Ischemic Stroke

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We examined the predictive value of clinical and radiological findings, including cerebral microbleeds (CMBs) seen in gradient-echo T2*-weighted magnetic resonance images, for hemorrhagic transformation (HT) following ischemic stroke, in ischemic stroke patients treated with recombinant tissue plasminogen activator (rt-PA). The subjects were 71 patients with acute ischemic stroke treated with rt-PA (50 males, 21 females; mean age +/- standard deviation 73 +/- 10 years; 53 cardiogenic stroke, 18 atherothrombotic).

HT on computed tomography (CT)(mean: 24 hours after onset) was seen in 26 (37%) subjects. The mean Alberta stroke programme early CT score on diffusion-weighted images (ASPECTS-DWI) score was significantly lower in the group with HT than that in the group without HT (6.5 +/- 2.3 vs 8.4 +/- 1.6, $P < 0.001$). Prevalence of CMBs was not significantly different between the groups with and without HT. Relative risk of various factors for appearance of HT was evaluated by logistic regression analysis. Increased ASPECTS-DWI score showed a significantly reduced relative risk for HT (odds ratio: 0.54, 95% confidence interval: 0.33–0.87), while the influence of CMBs (1.22, 0.23–6.53) was not significant.

In conclusion, ASPECTS-DWI score (a measure of the volume of ischemic tissue) is a useful marker for predicting HT. On the other hand, CMBs on T2*-weighted images may not be predictive for HT in patients treated with intravenous rt-PA.

Key words: ischemic stroke, magnetic resonance imaging, cerebral microbleeds, recombinant tissue plasminogen activator, hemorrhagic transformation

INTRODUCTION

Hemorrhagic transformation (HT) is a major concern in the acute stage of ischemic stroke, because it often results in a worse clinical outcome [1–7]. The introduction of recombinant tissue plasminogen activator (rt-PA) as a therapeutic agent in the acute stage of ischemic stroke, despite its well-established benefits, has resulted in an increasing risk of hemorrhagic complications, including HT [6, 7]. Thus, in considering thrombolytic therapy for acute ischemic stroke, it would be useful to have some means to predict the likelihood of development of HT [8–11].

Magnetic resonance imaging (MRI) using the gradient-echo T2*-weighted sequence has high sensitivity for iron-containing compounds, and is useful to detect cerebral microbleeds (CMBs), which contain hemosiderin [12]. Recent studies have indicated that CMBs detected in T2*-weighted images may be a predictor for symptomatic intracerebral hemorrhage [13–15]. Further, a significant association of CMBs with hemorrhagic transformation after ischemic stroke has been reported [16–18]. On the other hand, other reports have indicated that the presence of CMBs did not markedly increase the risk of HT in ischemic stroke patients treated with rt-PA [19–22]. However, among the latter group, only one relatively small study involved Japanese patients [22]. Therefore, we considered that a further study would be useful to assess the predictive value of clinical and radiological findings, including CMBs, for HT in Japanese patients treated with rt-PA. Here, we prospectively examined the relationship between various characteristics, including CMBs and HT, in acute ischemic stroke patients treated with rt-PA.

SUBJECTS AND METHODS

This study was approved by the clinical research committee of Tokai University School of Medicine (No 08R-050). The subjects in this study were 71 patients with acute ischemic stroke treated with rt-PA (50 males, 21 females; mean age +/- standard deviation 73 +/- 10 years) in Tokai University hospital between November 2007 and December 2011. Patients with history of hemorrhagic stroke, brain contusion or subdural hematoma were excluded from this study. The subtypes of ischemic stroke in the subjects were classified according to the criteria of the National Institute of Neurological Disorders and Stroke (NINDS-Ⅲ) as follows: cardiogenic, 53; atherothrombotic, 18. Among these subjects, 46 showed a lesion within the territory of middle cerebral artery (MCA), 14 in the territories of MCA plus anterior cerebral artery (ACA), and 11 in

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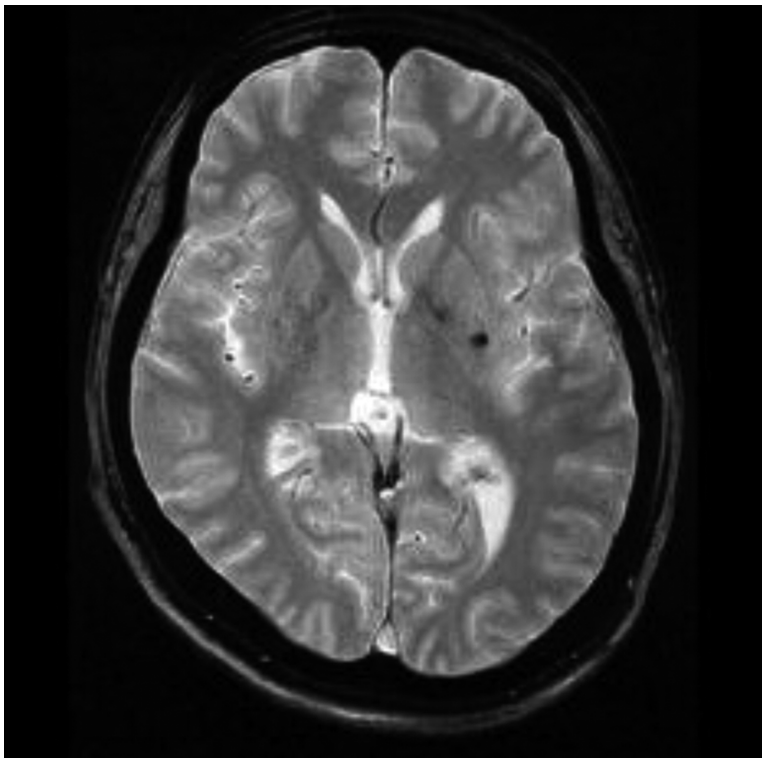

Figure Cerebral microbleed on gradient-echo T2*-weighted image
Cerebral microbleeds are represented as signal loss or hypointense lesion in the cerebral, cerebellar or brain stem region on gradient-echo T2*-weighted image.

the territory of vertebral-basilar artery (VBA) on MRI.

MR examinations were performed in all subjects with a 1.5-T magnet (Achieva, Philips, Eindhoven) using the gradient-echo T2*-weighted sequence. T1, T2-weighted, fluid attenuated inversion recovery (FLAIR), diffusion-weighted images were also obtained. CMBs were defined as signal loss or hypointense lesions in the cerebral or cerebellar parenchyma or brain stem on gradient-echo T2*-weighted images (for an example, see Figure). Areas of symmetric hypointensity in the globus pallidus, and signal loss involving branches of the middle, anterior and posterior cerebral artery were not included in CMBs. In the subjects having lesion in MCA territory, infarct volume was estimated according to the Alberta stroke programme early CT score on diffusion-weighted images (ASPECTS-DWI) [23]. ASPECTS-DWI score was estimated based on the ischemic involvement in two standardised axial slices. A high score indicates minimum ischemic involvement of these areas, while a low score indicates widespread ischemic involvement in MCA territory.

Magnetic resonance angiography was also performed by the three-dimensional time-of-flight method in all subjects. The intracranial arteries (internal carotid, a main trunk of the middle cerebral, basilar and vertebral arteries) were evaluated, based on source and reconstruction images. These MR examinations were conducted in all subjects before intravenous administration of rt-PA was started.

Computed tomographic (CT) examinations were firstly conducted during day 2 (mean: 24 hours after onset), and second examination was performed between day 4 and day 7 after admission. HT was evaluated in all subjects, based on CT images. It was defined according to NINDS criteria, as follows: acute infarction with punctate or variable hypodensity with an indistinct border within the vascular territory (HI) or typical homogeneous, hyperdense lesion with a sharp border with or without edema or mass effect (PH) [24].

Neurological deficits at admission were estimated using the National Institutes of Health stroke scale (NIHSS) score. The degree of disability at discharge from our hospital was classified according to the modified Rankin scale [25].

STATISTICAL ANALYSIS

Prevalences of subtypes of ischemic stroke, artery occlusion on MRA, MBs and prior use of antithrombotic agents between patients with and without HT were compared by using the chi-square test. Mean values +/- standard deviation of age, systolic blood pressure and time from stroke onset to administration of rt-PA between patients with and without HT were compared with Student's t-test, and DWI-ASPECTS and NIHSS scores between two groups were compared with the Mann-Whitney U-test. Odds ratios of variables (systolic blood pressure, NIHSS score, cardiogenic type, ASPECTS-DWI and CMBs) for HT were estimated by using logistic regression analysis.

RESULTS

The characteristics of the groups with and without HT are summarized in Table 1. HT on CT images was found in 26 (37%) subjects. Mean age, mean systolic blood pressure (mSBP), mean NIHSS score and mean onset-to-treatment time (i.e., time from stroke onset to starting the administration of rt-PA) were not significantly different between the groups with and without HT. However, the mean ASPECTS-DWI score was significantly lower in the group with HT than that in the group without HT (6.5 +/- 2.3 vs 8.4 +/- 1.6, $P < 0.001$). Prevalence of CMBs on T2*-weighted images, as well as history of antithrombotic therapy, subtypes or sites of BI, and artery occlusion on MRA were not significantly

Table 1 Profile in the groups with and without hemorrhagic transformation

	Patients without HT	Patients with HT	P value
Number of subjects	45	26	
Mean age (years)	72.6 +/- 9.1	73.7 +/- 11.2	0.674
Male	34 (76%)	16 (62%)	0.282
Prior antithrombotic agents	19(44%)	9 (41%)	> 0.999
Mean systolic blood pressure (mmHg)	163.4	168.8	0.505
Mean NIHSS score	14.6 +/- 7.0	16.1 +/- 6.6	0.360
Subtypes of BI			
Cardiogenic	34 (76%)	21 (81%)	0.771
Atherothrombotic	11(24%)	5 (19%)	
Sites of BI			
ACA	1 (2%)	1 (4%)	
MCA	34 (76%)	19 (73%)	
MCA + ACA	4 (9%)	2 (7%)	
VBA	6 (13%)	4 (16%)	
ASPECTS-DWI	8.4 +/- 1.6	6.5 +/- 2.3	< 0.001
Artery occlusion on MRA	34 (76%)	22 (85%)	0.548
CMBs +	8 (18%)	6 (23%)	0.758
Onset-to-treatment time (min)	147 +/- 23	137 +/- 27	0.079

Abbreviations: NIHSS, National Institutes of Health stroke scale, BI, brain infarction; ASPECTS-DWI, Alberta stroke programme early CT score on diffusion-weighted images; CMB, cerebral microbleed; HT, hemorrhagic transformation; ACA, anterior cerebral artery; MCA, middle cerebral artery; VBA, vertebral-basilar artery; MRA magnetic resonance angiography.

Table 2 Relationship between the number of cerebral microbleeds and hemorrhagic transformation

Number of CMBs	Patients without HT	Patients with HT		Total	P value
		HIs	PHs		
0	37 (65%)	15 (26%)	5 (9%)	57	
1−4	7 (58%)	4 (33%)	1 (8%)	12	0.377
≥ 5	1 (50%)	0	1 (50%)	2	

The relationship between the number of CMBs and HT was analyzed by using the chi-square test.
Abbreviations: HI, hemorrhagic infarct; PH: parenchymal hematoma, CMB, cerebral microbleed; HT, hemorrhagic transformation.

Table 3 Relative risks of several factors for hemorrhagic transformation

	Odds ratio	95% CI	P value
Systolic blood pressure	1.01	0.99−1.03	0.206
NIHSS score (per 1 point)	1.00	0.89−1.14	0.905
Cardiogenic	0.80	0.19−3.46	0.770
ASPECTS-DWI (per 1 point)	0.57	0.39−0.84	0.005
CMBs	0.66	0.12−3.64	0.206

Odds ratio were estimated by using logistic regression analysis.
Abbreviations: NIHSS, National Institutes of Health stroke scale, ASPECTS-DWI, Alberta stroke programme early CT score on diffusion-weighted images; CMB, cerebral microbleed; 95% CI, 95% confidence interval.

different between the two groups.

We next examined the relationship between the number of CMBs and the appearance of HT. The prevalence of the subjects with and without HT was not significantly different among the subgroups with the numbers of CMBs of 0 (35% vs 65%), 1−4 (42% vs 58%) and ≥5 (50% vs 50%) (Table 2).

Relative risks of several factors for HT on CT images are summarized in Table 3. Odds ratio of increasing ASPECTS-DWI score for the development of HT was significantly reduced (0.57, 95% confidence interval: 0.39-0.84, P=0.005). However, the odds ratio of CMBs (0.66, 0.12-3.64, P=0.206) showed no significance.

DISCUSSION

The relationship between CMBs on T2*-weighted images and HT after ischemic stroke has been examined by various investigators [16−22]. Prospective studies suggested that patients with CMBs on T2*-weighted images had significantly more frequent intracerebral hemorrhage after ischemic stroke [16−18]. However, among ischemic stroke patients with CMBs, rt-PA

treatment does not appear to further increase the risk of HT [19–22]. In this study, we found that the prevalence or number of CMBs was not significantly different between two groups of rt-PA-treated Japanese patients with and without HT. Further, the odds ratio of CMBs for the appearance of HT was not significantly increased. Since rt-PA (Alteplase is generally used in Japan) decays with a half-life of 10 min, and the duration of its intravenous administration is limited to 24 hours [10], it seems reasonable that intravenous rt-PA would not markedly increase the risk of HT in ischemic stroke patients with CMBs on T2*-weighted images.

The development of HT following ischemic stroke is considered to be correlated with severe neurological deficits [2, 8, 9], raised blood pressure [8], high levels of blood glucose [7, 8]. infarct size [2, 4, 7], and early ischemic changes on computed tomography (CT) [5, 11]. Treatment with intravenous rt-PA increases the risk of hemorrhagic complications, including HT [6, 7]. Among ischemic stroke patients treated with intravenous rt-PA, symptomatic intracerebral hemorrhage was encountered in 4~13% in the acute stage of stroke [8–10]. In patients treated with rt-PA, high signal intensity volume on DWI was an independent predictor of symptomatic intracerebral hemorrhage [8, 9, 11]. In this study, the relative risks of variables, including established markers for HT, were estimated by using logistic regression analysis. As a result, we found that ASPECTS-DWI score, reflecting infarct volume, was the only significant marker for HT among those examined. Thus, the volume of ischemic tissue may be a useful marker for predicting HT in patients treated with intravenous rt-PA.

In conclusion, the volume of ischemic tissue estimated in terms of ASPECTS-DWI score appears to be a useful marker for predicting HT. On the other hand, CMBs on T2*-weighted images may not be predictive for HT in patients treated with intravenous rt-PA.

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