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Intravenous Tissue Plasminogen Activator Thrombolysis in Patients without Major Arterial Occlusion Seems to Be Safe and Effective

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Key Words
Tissue plasminogen activator · Magnetic resonance angiography · Tissue plasminogen activator infusions, outcome

Abstract
Background: It is not clear whether tissue plasminogen activator (t-PA) thrombolysis in patients without major arterial occlusion is effective or safe. ***Methods:*** Consecutive anterior circulation stroke patients treated with t-PA within 3 h of onset were studied. The patients were divided into three groups according to magnetic resonance angiography findings before t-PA infusion: ICA group, ICA occlusion; MCA group, M1 and M2 occlusion, and no occlusion group. Clinical characteristics, the presence of hemorrhagic transformation on T_2* at 24 h after t-PA thrombolysis, and outcome at 3 months were compared among the three groups. ***Results:*** 112 patients were enrolled. The no occlusion group had 21 (18.8%) patients, the ICA group had 29 (25.9%), and the MCA group had 62 (55.4%). The frequency of hemorrhagic transformation was only 4.8% in the no occlusion group (31.0% for the ICA group, and 48.4% for the MCA group, p = 0.0012). At 3 months after t-PA therapy, 61.5% of the no occlusion group had a favorable outcome (modified Rankin score 0–1), which was the highest among the three groups (15.0% for the ICA group, and 41.5% for the MCA group, p = 0.0203). ***Conclusion:*** Intravenous t-PA therapy in acute stroke patients without major artery occlusion seems to be safe and effective.

Intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes in patients with acute ischemic stroke [1]. Early recanalization after t-PA infusion greatly improves stroke patients' outcomes [2–6]. However, it is not clear whether t-PA therapy in patients without major arterial occlusion is safe and effective.

Several previous studies using CT did not evaluate the occluded arteries before t-PA thrombolysis [7–12], therefore they likely included patients without major arterial occlusion. The NINDS study showed that t-PA thrombolysis was effective for lacunar stroke [1]. The majority of lacunar stroke patients might not have major artery occlusion, therefore it is possible that t-PA therapy in patients without major arterial occlusion is effective. Furthermore, the most important complication of t-PA therapy is symptomatic intracerebral hemorrhage (ICH) [13], and ICH was associated with large baseline DWI volume [14]. Therefore, it is possible that patients without major arterial occlusion who did not have large ischemic lesions

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are not likely to have hemorrhagic transformation, and t-PA thrombolysis for such patients is safe. This study aimed to elucidate whether t-PA therapy in patients without major arterial occlusion is safe and effective using magnetic resonance imaging (MRI) including magnetic resonance angiography (MRA) and T_2*.

Subjects and Methods

Consecutive patients with acute ischemic stroke treated with t-PA within 3 h of stroke onset between October 2005 and March 2010 were studied. Only patients thought to have anterior circulation ischemia were included in the present study. Patients who underwent mechanical thrombolysis for the occluded artery within 24 h after t-PA infusion were excluded. Patients with heart valve replacements, pacemakers, or clipping of cranial arteries were excluded, since MRI is contraindicated in such patients. The following clinical data were collected from all patients: (1) age and sex; (2) arterial blood pressure before t-PA infusion; (3) NIHSS score before and 24 h and 7 days after t-PA infusion; (4) presence of arterial occlusion on MRA before t-PA infusion; (5) baseline DWI-ASPECTS [15] before t-PA infusion; (6) presence or absence of early recanalization of occluded arteries within 1 h after the end of t-PA infusion; (7) vascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, and smoking; (8) presence of potential cardiac sources of emboli; (9) laboratory parameters before t-PA infusion; (10) administration of antithrombotic agents such as antiplatelet agents and warfarin, and (11) modified Rankin scale (mRS) score 3 months after t-PA therapy. The inclusion and exclusion criteria for intravenous t-PA were in accordance with the Japan Alteplase Clinical Trial [12]. The dose of t-PA was 0.6 mg/kg.

Before t-PA infusion, MRI studies, including diffusion-weighted imaging (DWI), MRA, and T_2*-weighted gradient echo imaging (T_2*), were performed to assess DWI-ASPECTS and to identify the occluded arteries and the presence of microbleeds. Next, follow-up MRI was performed 1 h after t-PA to identify the presence or absence of early recanalization and then again at 24 h to assess the presence of hemorrhagic transformation on T_2*. MRI was performed using a commercially available echo planar instrument on a 1.5-T unit (Signa Excite XL version 11.0; GE Healthcare, Milwaukee, Wisc., USA). The imaging protocol consisted of a T_2*-weighted gradient echo (repetition time 600 ms, echo time 17 ms, flip angle 30°) and diffusion-weighted echo planar (repetition time 8,000 ms, echo time 70 ms) imaging series, and intra- and extracranial MRA. The experienced researcher (K.K.) who evaluated the MRI findings was blinded to the patients' clinical background data.

The presence of major artery occlusion was assessed by MRA. Occluded arteries on initial MRA were identified as follows: M1 occlusion, M2 occlusion, and ICA occlusion. Recanalization was graded as complete, partial, or no recanalization, as follows: (1) complete recanalization, reappearance of the entire occluded artery and distal vessel branches; (2) partial recanalization, restoration of part of the distal vessel supplied by the occluded artery, and (3) no recanalization, persistent occlusion.

Microbleeds were defined as small, silent foci of signal loss on T_2* other than the principal lesions responsible for stroke episodes. Hemorrhagic transformation on T_2* at 24 h after t-PA infusion was defined as new appearance of low-intensity lesions on follow-up T_2* compared with initial T_2*.

NIHSS scores were obtained before, 24 h after, and 7 days after t-PA infusion by a neurologist. Three measures of clinical recovery based on modified methods used in previous studies were used [16]. 'Dramatic improvement' was defined as a $\geq$10 point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. 'Good improvement' was defined as a $\geq$4 point reduction in the total NIHSS score. 'Worsening' was defined as a $\geq$4 point increase in the total NIHSS score. Symptomatic cerebral hemorrhage was defined as an increase in the total NIHSS score of $\geq$4 if the ICH was likely to be the cause of clinical deterioration. Favorable and poor outcomes at 3 months after t-PA therapy were defined as mRS 0–1 and >3 or death, respectively.

To detect potential cardiac sources of emboli, all patients were examined using 12-lead electrocardiography, 24-hour electrocardiography monitoring, and transthoracic echocardiography. Transesophageal echocardiography was also performed if the patient's condition was suitable. The following potential emboligenic cardiac diseases were considered: atrial fibrillation, previous acute myocardial infarction, mitral valve disease, and dilated cardiomyopathy.

The patients were divided into three groups according to their initial MRA findings: the ICA group had patients with ICA occlusion; the MCA group had patients with M1 and M2 occlusion, and the no occlusion group had patients without major arterial occlusion. The baseline clinical characteristics, presence of hemorrhagic transformation, and mRS score 3 months after t-PA therapy were compared among the three groups. Furthermore, in non-occluded group, patients were divided into four subgroups according to area and size of ischemic lesions on initial DWI; cortical lesion, subcortical lesion of diameter $\geq$15 and <15 mm and non-lesion. We then compared neurological recovery at the acute phase of stroke and patient outcome at 3 months after stroke onset among four groups. The significance of inter-group differences was assessed using Fisher's exact test for categorical variables and the Mann-Whitney U test and Kruskal-Wallis U test for continuous variables. A value $p < 0.05$ was considered statistically significant. Statistical analysis was performed using StatView version 5 statistical software. All study protocols followed the principles outlined in the Declaration of Helsinki, and informed consent was obtained from all patients.

Results

A total of 159 consecutive stroke patients were treated with t-PA. Three patients were excluded due to the presence of a pacemaker, and 38 patients had posterior circulation strokes. Six patients who underwent mechanical thrombolysis for the occluded artery 1 h after t-PA infusion were excluded. As a result, 112 patients (58 men, 54 women; mean age 75.7 ± 9.9 years) were enrolled in the present study. Durations between symptom onset and

Table 1. Baseline clinical data of patients with ICA occlusion, MCA occlusion, and no occlusion

	ICA (n = 29)	MCA (n = 62)	No occlusion (n = 21)	p
Age, years	78.4 ± 8.4	75.6 ± 10.2	72.3 ± 10.1	0.4221
Female (%)	14 (48.3)	32 (51.6)	8 (38.1)	0.5632
Time from symptom onset to treatment, min	143.8 ± 26.6	138.6 ± 32.7	153.1 ± 19.9	0.2922
Risk factors (%)				
Hypertension	16 (55.2)	45 (72.6)	13 (61.9)	0.238
Diabetes mellitus	6 (20.7)	11 (17.7)	6 (28.6)	0.5689
Hyperlipidemia	4 (13.8)	10 (16.1)	6 (28.6)	0.3506
Smoking	13 (44.8)	18 (29.0)	11 (52.4)	0.103
Atrial fibrillation	18 (62.1)	41 (66.1)	2 (9.5)	<0.0001
Systolic blood pressure, mm Hg	156.1 ± 18.5	153.3 ± 22.8	155.7 ± 25.2	0.8218
Diastolic blood pressure, mm Hg	82.8 ± 17.8	82.7 ± 14.8	83.2 ± 19.1	0.9772
Glucose, mg/dl	153.2 ± 52.3	146.5 ± 40.4	144.0 ± 48.5	0.6976
Use of antiplatelet therapy (%)				
Warfarin	4 (13.8)	8 (12.9)	1 (4.8)	0.5500
Aspirin	6 (20.7)	16 (25.8)	6 (28.6)	0.4948
Stroke type (%)				
Cardioembolic stroke	17 (58.6)	43 (69.4)	4 (19.0)	<0.0001
Large artery diseases	7 (24.1)	0	0	0.1823
Lacunar	0	0	4 (19.0)	0.0001
Undetermined stroke	5 (17.2)	19 (30.6)	13 (61.9)	0.0034
Early recanalization	8 (27.6)	28 (45.2)	NA	
NIHSS score				
Baseline	19.1 ± 5.5	14.9 ± 6.7	8.5 ± 4.5	<0.0001
24 h after	15.5 ± 8.3	10.9 ± 9.4	5.4 ± 7.0	0.0002
7 days after	16.7 ± 11.7	9.4 ± 9.5	6.0 ± 7.9	0.0014
mRS at 3 months after t-PA therapy[1], %				
mRS 0–1	10 (2/20)	35.8 (19/53)	61.6 (8/13)	0.0081
mRS 4–6	25 (15/20)	47.2 (25/53)	30.8 (4/13)	0.0294
ASPECTS	6.6 ± 2.7	7.5 ± 2.1	9.6 ± 0.5	<0.0001
Microbleeds (%)	6 (20.7)	11 (17.7)	6 (28.6)	0.5689

[1] 26 patients with mRS >1 were excluded.

initial MRI study and t-PA bolus were 100.0 ± 41.5 and 142.7 ± 29.5 min, respectively.

Initial MRA demonstrated no major brain arterial occlusion in 21 patients (no occlusion group, 18.8%). The remaining 91 (81.3%) patients had an occluded artery: M1 occlusion in 40 patients, M2 in 22, and ICA in 29. Thus, the ICA and MCA groups had 29 (25.9%) and 62 (55.4%) patients, respectively. Table 1 shows the baseline clinical characteristics of the three groups. Atrial fibrillation was less frequently observed in the no occlusion group than in the other two groups (9.5% for no occlusion group, 62.1% for ICA group, and 66.1% for MCA group, $p < 0.0001$). The ASPECTS score was highest in the no occlusion group (9.6 ± 0.5 for the no occlusion group, 6.6 ± 2.7 for the ICA group, and 7.5 ± 2.1 for the MCA group, $p < 0.0001$). No other factors differed among the three groups.

At 24 h after t-PA infusion, 40 patients (35.7%) showed hemorrhagic transformation on T_2*. Symptomatic ICH was observed in 2 patients within 24 h after t-PA infusion. The no occlusion group had the lowest frequency of hemorrhagic transformation (4.8% for the no occlusion group, 31.0% for the ICA group, and 48.4% for the MCA group, $p = 0.0012$; fig. 1).

The initial, 24 h after, and 7 days after t-PA therapy NIHSS scores were lowest in the no occlusion group (baseline 8.5 ± 4.5 for the no occlusion group, 19.1 ± 5.5 for the ICA group, and 14.9 ± 6.7 for the MCA group, $p < 0.0001$; 24 h, 5.4 ± 7.0, 15.5 ± 8.3, and 10.9 ± 9.4, $p = 0.0002$, and 7 days, 6.0 ± 7.9, 16.7 ± 11.7, and 9.4 ±

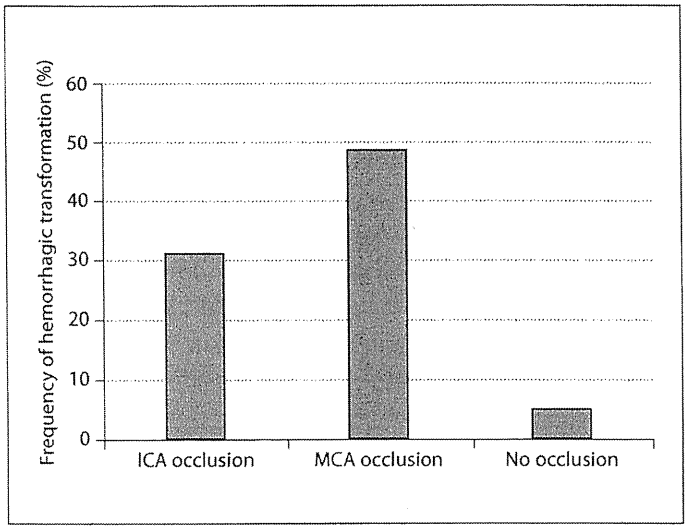

Fig. 1. Frequency of hemorrhagic transformation on T_2*, 24 h after t-PA infusion by group.

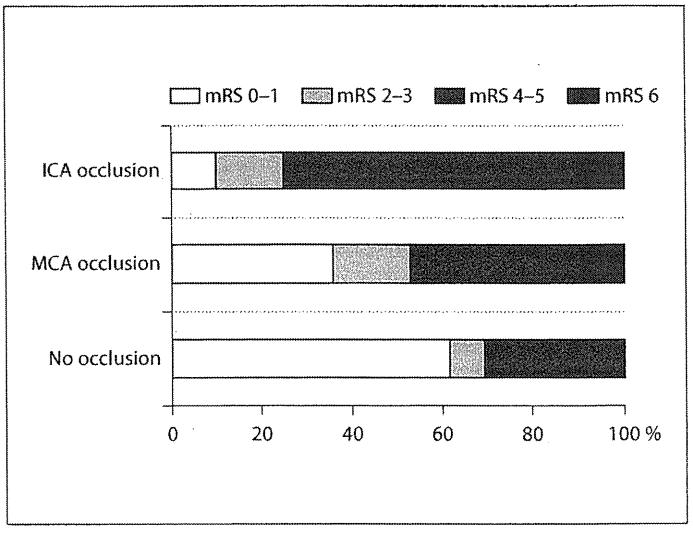

Fig. 2. mRS scores 3 months after t-PA therapy by group, after exclusion of 26 patients with mRS scores >1 before t-PA infusion.

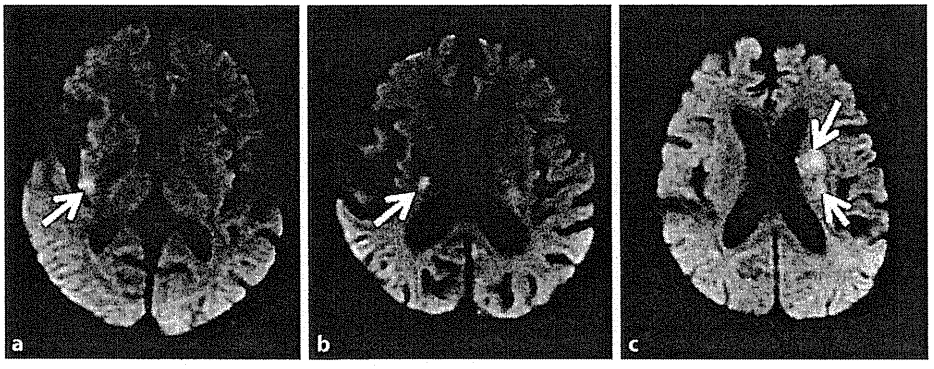

Fig. 3. Initial DWI before t-PA infusion: **a** cortical lesion, **b** subcortical lesion of diameter <15 mm, and **c** subcortical lesion of diameter ≥15 mm.

9.5, p = 0.0014). At 24 h after t-PA therapy, 35 (31.3%) patients had dramatic improvement, 27 (24.1%) patients had good improvement, 37 (33.0%) patients had no change, and 13 (11.6%) patients had worsening. The no occlusion group had dramatic improvement more frequently than the other groups, but the difference was not significant (42.9% for the no occlusion group, 17.2% for the ICA group, and 33.9% for the MCA group, p = 0.1247). On the other hand, worsening was not different among the three groups (9.5% for the no occlusion group, 6.9% for the ICA group, and 14.5% for the MCA group, p = 0.5413).

At 3 months after t-PA therapy, 30 (26.8%) patients had favorable outcomes, and 65 (58.0%) patients had poor outcomes. When we excluded 26 patients with mRS scores >1 before t-PA infusion, of 86 patients, 29 (33.7%) had favorable outcomes, and 44 (51.2%) had poor outcomes. Favorable outcomes were most frequent in the no occlusion group (61.5% for the no occlusion group, 15.0% for the ICA group, and 41.5% for the MCA group, p = 0.0203; fig. 2). Poor outcomes were least frequent in the no occlusion group (9.1% for the no occlusion group, 34.1% for the ICA group, and 56.8% for the MCA group, p = 0.0294; fig. 2).

In 21 patients with non-occluded group, 4 patients had cardioembolic stroke, 4 had small-vessel diseases, and remaining 13 patients had undetermined stroke (table 1). Initial DWI demonstrated 2 patients in cortical lesion, 7 in subcortical lesion of diameter ≥15 mm, 6 in subcortical lesion of diameter <15 mm and 6 in non-lesion. Figure 3 shows representative cases. Of 4 patients with cardioembolic stroke, 2 had cortical lesion, 1 had subcortical lesion of diameter <15 mm in 1, and 1 had non-lesion. Of

Table 2. Neurological recovery at acute phase of stroke and mRS 3 months after t-PA therapy for initial DWI findings in patients with no arterial occlusion before t-PA infusion

	Cortical lesion (n = 2)	Subcortical lesion		Non-lesion (n = 6)
		∅ <15 mm (n = 6)	∅ ≥15 mm (n = 7)	
24 h after t-PA infusion				
Dramatic recovery	1	4	2	2
Good recovery	1	0	0	2
Worsening	0	0	2	0
7 days after t-PA infusion				
Dramatic recovery	1	4	2	2
Good recovery	0	0	1	0
Worsening	1	0	3	1
mRS 3 months after t-PA infusion[1]	(n = 2)	(n = 5)	(n = 4)	(n = 2)
0–1	1	4	2	1
4–6	1	0	2	1

[1] 8 patients with mRS >1 before t-PA infusion were excluded.

13 patients with undetermined stroke, 7 had subcortical lesion of diameter ≥15 mm, 1 had subcortical lesion of diameter <15 mm, and 5 had non-lesion. All of the small-vessel diseases had a subcortical lesion of diameter <15 mm. Regarding stroke subtype, dramatic improvement 24 h and 7 days after t-PA therapy was observed in 2 and 3 of 4 patients with cardioembolic stroke, 3 and 2 of 4 with small-vessel diseases, and 4 and 6 of 13 with undetermined stroke, respectively ($p = 0.2799$ and $p = 0.5970$). Worsening at 24 h was observed in only 2 (15.4%) of undetermined stroke, but 7 days 4 patients of undetermined and 1 patient of cardioembolic stroke had worsening. When 8 patients with mRS >1 before t-PA therapy were excluded, mRS at 3 months after t-PA therapy was 3 patients in mRS of 0, 5 in mRS of 1, 0 in mRS of 2, 1 in mRS of 3, 2 in mRS of 4, 2 in mRS of 5, and 0 in mRS of 6, respectively. Favorable and poor outcome was present in 2 and 1 of 3 patients with cardioembolic stroke, 2 and 0 of 3 with small-vessel diseases, and 4 and 3 of 7 with undetermined stroke. Table 2 shows neurological recovery at acute phase of stroke and patient outcome 3 months after t-PA therapy for initial DWI findings before t-PA infusion. Dramatic improvement 24 h and 7 days after t-PA therapy was observed in 1 and 1 of 2 patients with cortical lesion, 4 and 4 of 6 with subcortical lesion of diameter <15 mm, 2 and 2 of 7 with subcortical lesion of diameter ≥15 mm, and 2 and 4 of 6 with non-lesion, respectively ($p = 0.5249$ and $p = 0.2577$). Worsening at 24 h was observed in only 2 patients of subcortical lesion of diameter ≥15 mm ($p = 0.2194$), but 7 days 3 patients of subcortical lesion of diameter ≥15 mm, 1 of cortical lesion, and 1 of non-lesion patients had worsening. However, any patients with subcortical lesion of diameter <15 mm did not have worsening 24 h and 7 days after t-PA therapy at all. When 8 patients with mRS >1 before t-PA therapy were excluded, favorable and poor outcome were present in 1 and 1 of 2 patients with cortical lesion, 2 and 2 of 7 patients with subcortical lesion of diameter ≥15 mm, and 4 and 0 of 6 patients with subcortical lesion of diameter <15 mm and 1 and 1 of 2 patients with non-lesion, respectively ($p = 0.7602$ and $p = 0.3066$). As a result, any patients with subcortical lesion of diameter <15 mm did not have worsening at acute phase of stroke and poor outcome at 3 months after t-PA infusion. However, 3 of 7 patients with subcortical lesion of diameter ≥15 mm had worsening ($p = 0.1923$) and 2 of 4 had poor outcome ($p = 0.1667$).

Discussion

The present study demonstrated that the frequency of hemorrhagic transformation of the no occlusion group was only 4.8%, the lowest among the three groups. Furthermore, at 3 months after t-PA therapy, 61.5% of the no occlusion group had a favorable outcome, the highest among the three groups.

The most important complication of t-PA therapy is symptomatic ICH. In the Japan Alteplase Clinical Trial study, CT demonstrated symptomatic ICHs in 5.8% of patients and asymptomatic ICHs in 31% of patients with-

in 10 days of t-PA treatment [12]. In the present study, the frequency of hemorrhagic transformation in patients without major arterial occlusion was 4.8%, which was very low. On the other hand, hemorrhagic transformation was seen in 31.0% of the ICA group and 48.4% of the MCA group. Thus, t-PA therapy in patients without major arterial occlusion should be safe.

In the present study, patients without a major artery occlusion more frequently had favorable outcomes (mRS score 0–1) than those with a major artery occlusion. However, we did not have randomized patients treated with placebo and therefore it is not possible to state that intravenous t-PA therapy is effective in stroke patients without major artery occlusion. Furthermore, the number of our t-PA patients without major artery occlusion was quite small and therefore their more common favorable outcome could also be a play of chance.

When we see acute stroke patients without occluded arteries on MRA within 3 h of onset, we consider them as having a small cortical infarction, lacunar stroke, or early recanalization of occluded arteries. Furthermore, some might have M3 and M4 occlusion, which MRA cannot always evaluate. t-PA may be effective for such patients because t-PA is more likely to recanalize M3 and M4 occlusion than MCA and ICA occlusion.

In patients with subcortical lesion without major artery occlusion, lesion size of diameter ≥15 mm tended to have worsening at the acute phase of stroke and poor outcome 3 months after t-PA compared to diameter <15 mm (small-vessel diseases) (42.9 vs. 0%, $p = 0.1923$, and 50.0 vs. 0%, $p = 0.1667$). Unfortunately, although the discrepancy did not reach a significant difference statistically because of small number, t-PA therapy was not effective for subcortical lesion of diameter ≥15 mm. Caplan [17] proposed that such ischemic infarction was termed as branch atheromatous disease and neurological deterioration at acute phase of stroke was frequently seen and patient outcome was relatively poor. Therefore, we suspected that subcortical lesion of diameter ≥15 mm without major artery occlusion, which was considered as branch atheromatous disease, might be resistant for t-PA therapy. We should need a more large number of patients study to confirm this hypothesis.

In the present study, at 24 h after t-PA therapy, 42.9% of the no occlusion group had dramatic improvement, and at 3 months after t-PA therapy, 61.5% had a favorable outcome. The NINDS study [1] showed that in patients with small-vessel occlusion, who were thought to be similar to our patients without major arterial occlusion, the frequency of a favorable outcome at 3 months was 63% in the t-PA-treated group and 40% in the placebo group. Therefore, we believe that t-PA therapy in patients without major artery occlusion seems to be effective.

The present study had several limitations. Firstly, MRA was used to assess the occluded artery. MRA is somewhat inaccurate for detecting vessel occlusion or stenosis [18]. Secondly, MRI cannot be performed in patients with implantation of metallic materials, such as pacemakers and metal clips. In fact, 3 patients were excluded from our study for this reason. Thirdly, the rates of hemorrhagic transformation may have been lower because the dose of t-PA (0.6 mg/kg in Japan) is lower than the internationally approved dosage of 0.9 mg/kg [12]. Finally, our study had a relatively small number of patients.

In conclusion, the frequency of hemorrhagic transformation was very low in the no occlusion group. In the no occlusion group, 42.9% had dramatic improvement, and 61.5% had a favorable outcome. Therefore, intravenous t-PA therapy in acute stroke patients without major occluded arteries seems to be safe and effective.

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Acute Stroke Patients Have Occult Malignancy More Often than Expected

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Key Words
Acute ischemic stroke · Occult malignancy · Nonbacterial thrombotic endocarditis

Abstract
The aim of the present study was to investigate the frequency of having occult malignancy in patients with acute ischemic stroke and their clinical characteristics. We retrospectively enrolled 1,714 consecutive ischemic stroke patients within 7 days of onset. The patients were divided into two groups: the Non-M group had no malignancy, and the M group had malignancy. We compared the clinical characteristics of the two groups. Of 1,714 ischemic stroke patients, 51 patients (3.0%; M group) were newly diagnosed as having malignancy. The M group was significantly older than the Non-M group ($p = 0.009$). Hemoglobin (Hb) was less and D-dimer was higher in the M group than in the Non-M group ($p < 0.001$). The patients with both D-dimer ≥1.3 ng/dl and Hb <12.8 g/dl more frequently had occult malignancy than patients without ($p = 0.0088$).

Introduction

Cancer and stroke are the second and third leading causes of death, respectively, in Japan. Both disorders increase in incidence and prevalence with age. In patients with cancer, stroke frequently occurs. Graus et al. [1] found evidence of cerebral infarction in 7% of 3,426 autopsied cancer patients. Nonbacterial thrombotic endocarditis (NBTE) is the most common cause of stroke in cancer patients [2–4]. It is thought to occur via a state of chronic disseminated intravascular coagulation (DIC) that predisposes cardiac valves to edema, degeneration and deposition of sterile platelet-thrombin vegetation [5]. Cerebral intravascular coagulation is the second most common mechanism of stroke in cancer patients. However, such a mechanism of stroke frequently occurs in the terminal stage of malignancy [6–8].

Cancer-related stroke can occur at any point during the course of malignancy [9]. In fact, in a few patients, stroke is the first manifestation of occult malignancy. If occult malignancy in patients with acute stroke could be identified and treated, the patients' prognosis should improve. Therefore, it is important to search for occult malignancy in acute stroke patients. The aim of the present study was to investigate the frequency of occult malignancy in patients with acute ischemic stroke and their clinical characteristics.

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Participants and Methods

Acute ischemic stroke patients admitted to our stroke center (Stroke Center, Kawasaki Medical School, Kurashiki, Japan) within 7 days of stroke onset between March 2004 and August 2009 were retrospectively studied. All patients had a baseline clinical assessment on admission with ECG, chest X-ray, abdominal X-ray, and brain CT or MRI, including diffusion weighted imaging, fluid-attenuated inversion-recovery images, T2*-weighted imaging and MR angiography. All patients underwent duplex carotid sonography to evaluate stenotic carotid lesions. Blood samples for measurement of hemoglobin (Hb), WBC, D-dimer, fibrinogen, AST, ALT and C-reactive protein were obtained at baseline.

Information about patient history, including cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia and smoking), atrial fibrillation (AF) and malignancy history, was obtained. Cardiovascular risk factors were defined as follows: (1) hypertension, use of antihypertensive agents, systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg on admission; (2) diabetes mellitus, use of oral hypoglycemic agents or insulin or glycated Hb >6.4%; (3) hyperlipidemia, use of antihyperlipidemic agents or serum cholesterol level >220 mg/dl; and (4) smoking or any lifetime cigarette use. Patients with previous malignancy that had been treated and from which they had recovered completely were excluded from this study. Thus, only stroke patients who had not previously been diagnosed as having cancer were enrolled.

Using Trial of ORG 10172 in Acute Stroke Treatment criteria [10], ischemic stroke subtypes were categorized into five groups: (1) large-artery atherosclerosis; (2) cardioembolism; (3) small-artery occlusion (lacune); (4) stroke of other determined etiology; and (5) stroke of undetermined etiology. Diagnoses are based on clinical features and data collected by tests such as brain imaging (CT/MRI), cardiac imaging (echocardiography, Holter ECG, etc.), duplex imaging of extracranial arteries, angiography, contrast-transcranial Doppler examination and laboratory assessments for a prothrombotic state.

Transesophageal echocardiography (TEE) was done to detect right-to-left shunt (RLS) and NBTE [2–4, 11]. Venous ultrasonography of the lower limb was carried out to detect deep venous thrombus.

Malignancy Survey

Patients had fecal occult blood tests, chest X-rays and laboratory data as routine tests. If patients had positive fecal occult blood tests, a search for malignancy was conducted using tumor markers (CEA, carbohydrate antigen 19-9, prostate-specific antigen for men, carbohydrate antigen 125 for women), abdominal echography, abdominal CT, gastroscopy and colonoscopy. If patients had suspected lung cancer on chest X-ray, contrast chest CT was performed. When malignancy was diagnosed, it was evaluated using the TMN staging system.

Statistical Methods

All patients were divided into two groups: the no malignancy group (Non-M group) and the newly diagnosed malignancy group (M group). All data were entered into SPSS software (Version 13.0 for Windows) for storage and analysis. Baseline characteristics and laboratory data were compared between the two groups using the Mann-Whitney U test and the χ^2 test. If there were significant differences in continuous variables between the Non-M and M groups, the optimal cutoff points of each continuous variable to discriminate the Non-M group from the M group were obtained by receiver operating characteristic (ROC) curves. Differences were considered statistically significant at $p < 0.05$.

Table 1. Baseline characteristics and laboratory data for the two groups

	Non-M n = 1,663	M n = 51	p
Age, years (median)	73	77	0.009
Male, n (%)	1,044 (63)	30 (59)	0.565
TIA, n (%)	252 (15)	11 (22)	0.211
Ischemic stroke, n (%)	1,411 (85)	40 (78)	0.211
Small-vessel disease	243 (15)	4 (8)	0.157
Cardioembolic stroke	440 (26)	16 (31)	0.434
Large-vessel disease	130 (8)	5 (10)	0.604
Other determined etiology	54 (32)	5 (10)	0.011
Undetermined etiology	544 (33)	10 (20)	0.048
Hypertension, n (%)	1,115 (67)	32 (63)	0.492
Hyperlipidemia, n (%)	506 (30)	13 (25)	0.431
Diabetes mellitus, n (%)	443 (27)	13 (25)	0.858
Smoking, n (%)	777 (47)	16 (31)	0.029
AF, n (%)	346 (21)	15 (29)	0.142
RLS/TEE, n (%)	401/1,020 (39)	17/30 (57)	0.056
Hb (median), g/dl	13.4	12.1	<0.001
WBC (median), /μl	6,430	6,390	0.925
CRP (median), mg/dl	0.13	0.21	0.499
AST (median), IU/l	21	20	0.327
ALT (median), IU/l	17	18	0.535
Fibrinogen (median), mg/dl	254	293	0.662
D-dimer (median), ng/dl	0.9	1.6	<0.001
Fecal occult blood test, n (%)	232/578 (40)	26/48 (54)	0.058

Mann-Whitney U test, χ^2 test.

Results

A total of 1,822 consecutive ischemic stroke patients were admitted to our stroke center between March 2004 and August 2009. Of these, 108 patients had a history of a malignancy for which they had been treated and recovered completely. Thus, a total of 1,714 consecutive patients (1,074 male; mean age 71.5 years) were enrolled in the present study.

During hospitalization, 51 patients (3.0%; M group) were newly diagnosed as having occult malignancy. Table 1 shows the type of cancer. The cancers were located in the colon in 13 patients, in the stomach in 10, in the lung in 6, in the liver in 4, in the pancreas in 4, in the bile duct in 4, in the prostate in 4, in the kidney in 3, in the uterus in 3, in the breast in 1 and in the ovary in 2. The

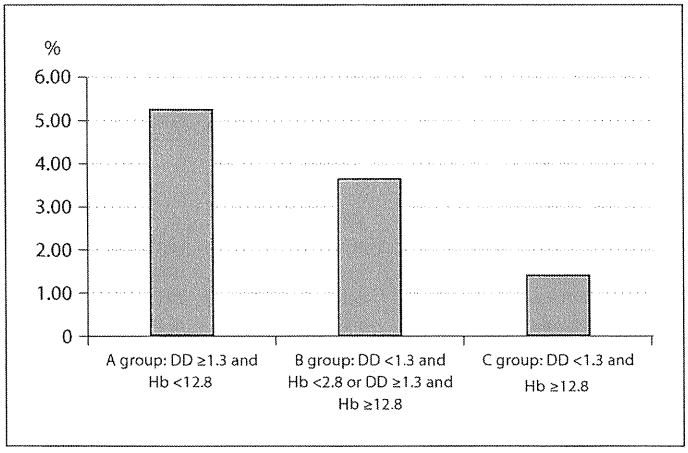

Fig. 1. The frequency of occult malignancy in the three subgroups.

Table 2. Type of cancer in the M group (n; total n = 51)

Colon	13
Liver	4
Pancreas/bile duct	4
Kidney	3
Bladder	1
Prostate	4
Stomach	10
Lung	6
Uterine	3
Breast	1
Ovary	2

histological types were as follows: adenocarcinoma (n = 42), squamous cell carcinoma (n = 5) and hepatocellular carcinoma (n = 4). The diagnostic modality that most often revealed cancer was fecal occult blood testing (n = 20), followed by abdominal echography (n = 10), abdominal CT (n = 10), chest CT (n = 6), prostate-specific antigen (n = 4) and chest X-ray (n = 1).

Table 1 shows the clinical characteristics of the two groups. The M group was significantly older than the Non-M group (77 vs. 73 years; p = 0.009). The M group less frequently had other determined and undetermined etiology than the Non-M group (54 vs. 5; p = 0.011, 544 vs. 10; p = 0.048). Risk factors excluding smoking were not different between the two groups. Hb was less and D-dimer was higher in the M group than in the Non-M group (12.1 vs. 13.4 g/dl, p < 0.001; and 1.6 vs. 0.9 ng/dl, p < 0.001). The normal range of Hb value has a gender gap: 13.5–17.5 g/dl for men, 11.5–15.0 g/dl for women. Taking gender differences into account, Hb was less in the M group than in the Non-M group (men: 14.1 vs. 13.5 g/dl, p = 0.024; women: 12.6 vs. 11.1 ng/dl, p < 0.001). Of 626 patients (37%) assessed by fecal occult blood testing, 258 (41.2%) had positive fecal occult blood. Of these, 26 patients (10.1%) had malignancy. TEE was performed in 1,050 patients (61%). No vegetations were detected, and no patients had NBTE. RLS was higher in the M group than in the Non-M group on TEE (57 vs. 39%, p = 0.056), but the difference was not significant.

Using ROC curves, the optimal cutoff points of Hb and D-dimer to discriminate the Non-M group from the M group were 12.8 g/dl and 1.3 ng/dl, respectively. The patients were divided into three subgroups according to D-dimer ≥ and <1.3 ng/dl and Hb ≥ and <12.8 g/dl: A group, both D-dimer ≥1.3 ng/dl and Hb <12.8 g/dl; B group, both D-dimer <1.3 ng/dl and Hb <12.8 g/dl or both D-dimer ≥1.3 ng/dl and Hb ≥12.8 g/dl; C group, both D-dimer <1.3 ng/dl and Hb ≥12.8 g/dl. The frequency of the presence of occult malignancy was 5.3% (19/361) in the A group, 3.9% (23/592) in the B group and 1.4% (12/841) in the C group (p < 0.001; fig. 1). Therefore, the patients with both D-dimer ≥1.3 ng/dl and Hb <12.8 g/dl more frequently had occult malignancy than patients without both [19/361 (5.3%) vs. 35/1398 (2.4%); p = 0.0088].

Discussion

The present study demonstrated that the frequency of occult malignancy diagnosed during hospitalization was at least 3.0%. The incidence of colorectal cancer has been reported to be 16 per 10,000 person-years for the general population of Japan [12]. In the present study, colon cancer was newly diagnosed in 13 patients (0.76%), for an incidence that was about 500 times that for general examinations in Japan. Thus, we believe that the prevalence of occult malignancy was higher than expected in acute stroke patients.

Patients with malignancy had elevated D-dimer and lower Hb levels [13–21]. The present results demonstrated that patients with D-dimer ≥1.3 ng/dl and Hb <12.8 g/dl on admission more frequently had malignancy than those without both. Explanations for the decrease in Hb level in the M group are as follows. First, some of the patients with malignancy had cancer cachexia. Second, some patients had gastrointestinal cancers and bleeding. In fact, 100% of patients with gastrointestinal cancer had positive fecal occult blood tests.

Previous reports showed that D-dimer levels were associated with NBTE and DVT in cancer patients [17–21]. Edoute et al. [18] reported that D-dimer levels increased in patients with NBTE. However, no patients had NBTE in the present study. Almost all patients with cancer show laboratory evidence of hypercoagulability. Naschitz et al. [5] reported that occult cancer promotes plaque rupture or erosion, releases microparticles from platelets and enhances thrombin formation. Thus, our patients with malignancy had elevated D-dimer levels.

In the present study, colon cancer was the most frequent cancer, followed by stomach cancer. Chaturvedi et al. [6] reported that in 33 patients with cancer-related stroke (Trousseau's syndrome), lung cancer was observed in 9 (27%) and gynecological cancer was observed in 7 (21.2%). Cestari et al. [7] reported that in stroke patients with cancer, lung (30%), brain (9%) and prostate (9%) were the most common cancers. However, these reports included patients who had been treated before stroke onset, but not patients with newly diagnosed occult malignancy after stroke onset. Therefore, the cancer lesions differed between the present and previous studies. Furthermore, in acute ischemic stroke, antiplatelet and anticoagulation therapy was started immediately after admission. Therefore, fecal occult blood tests may likely be positive in patients with potential cancers of digestive organs, such as colon cancer.

The M group demonstrated a trend toward higher rates of RLS ($p = 0.056$). Iguchi et al. [22] reported that RLS was more frequent in patients with malignancy than in patients without malignancy. Paradoxical brain embolism should be considered an important mechanism in patients with stroke with malignancy. We believe that the stroke mechanism of some patients with occult malignancy was paradoxical brain embolism. Taccone et al. [23] reported that acute stroke patients having occult malignancy were 52.4 years old and the most frequent neoplasms were lung and breast cancer. Rogers [24] reported that NBTE and DIC may cause the cerebral infarction in a hypercoagulable state. In our study, the median age of the M group was 77, and the most frequent neoplasms were colon and stomach cancer, NBTE was not found out at TEE and only three patients had DIC. Because many patients were assessed by fecal occult blood testing, abdominal echography and abdominal CT, most frequently neoplasms were tumors of digestive organs. The cancers were detected earlier, and early stage cancers were 57% in the M group. Therefore, the median age of the M group was higher, and NBTE and DIC were less detected.

The present study had some limitations. First, this was a retrospective study, and obstetrical and gynecological surveys were not conducted. Second, after hospital discharge, patients without malignancy were not examined. Thus, the frequency of malignancy might be greater than reported. Third, the methylenetetrahydrofolate reductase (MTHFR mutations) [25, 26], folic acid deficiency [27], Leiden factor V [25, 26] and thrombin gene mutations were not examined in the M group.

In conclusion, at least 3.0% of acute ischemic stroke patients had occult malignancy. The presence of both D-dimer ≥ 1.3 ng/dl and Hb <12.8 g/dl on admission appears to be a good predictor for malignancy in acute stroke patients.

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原著

片側舞踏アテトーゼ運動を呈した大脳皮質の心原性脳塞栓症の1例*

植村順一** 芝崎謙作** 井上 剛**
井口保之** 木村和美**

Key Words : hemichoreoathetosis, cerebral cortex, cardioembolic stroke, reperfusion, hyperemia

はじめに

脳梗塞による片側舞踏アテトーゼ運動の報告例は散見されるが[1)~3)]，責任病巣として基底核がほとんどである．われわれは，片側舞踏アテトーゼ運動を呈し，大脳皮質に脳梗塞をきたした心原性脳塞栓症例を経験したので報告する．

症　例

患者：58歳，男性(右手利き)．

主訴：言葉が出ない，右手足の不随意運動．

生活歴：喫煙歴はある(1日20本を30年間)．

既往歴：55歳時に脳梗塞(左島皮質)，心房細動，橋本病．

現病歴：2006年12月20日午前9時30分起床時に言葉が出なくなり，右手足が意志に関係なく動くことを自覚した．午前11時に当科外来を受診し即日入院した．

入院時現症：身長170cm，体重79kg．血圧136/114mmHg，脈拍150/分・不整，体温36.2℃．心尖部に拡張期雑音を聴取した．神経学的所見では，意識はJapan Coma Scale I-3，簡単な物品呼称は可能であるが二語文は非流暢で運動性失語であった．眼球は左側へ共同偏位し，右側への注視麻痺を認めた．瞳孔は正円同大，対光反射は正常であった．軽度の中枢性右顔面神経麻痺を認めたが，以前の脳梗塞の後遺症によるものであった．Barré徴候，Mingazzini徴候は正常で，四肢の筋トーヌスは低下していた．右上肢は不規則に前腕をゆっくり捻転させるアテトーゼ運動とすばやく前腕を屈曲させる舞踏運動を認めた．また，右下腿を不規則に伸展，足指を伸展，屈曲させるアテトーゼ運動を認めた．不随意運動は安静時に頻度が減少し，計算や言葉の復唱で増強した．深部感覚障害はなく，視覚による改善も認めなかった．深部反射は四肢で減弱し，病的反射はなかった．協調運動，自律神経系に異常はなかった．

検査所見：血算に異常なく，生化学でCK 737 IU/*l*と上昇していた．凝固・線溶系マーカーは正常であった．甲状腺機能はTSH 24.41μIU/m*l*，FT4 0.68ng/d*l*，FT3 2.09pg/m*l*と低下していた．抗サイログロブリン抗体1,600倍，抗マイクロソーム抗体6,400倍，抗TPO抗体70.6倍と異常高値であった．リウマチ因子，抗核抗体，ループスアンチコアグラント，抗カルジオリピンβ2-GPI抗

* Hemichoreoathetosis associated with cerebral cortex in cardioembolic infarction. A case report. (Accepted April 27, 2010).

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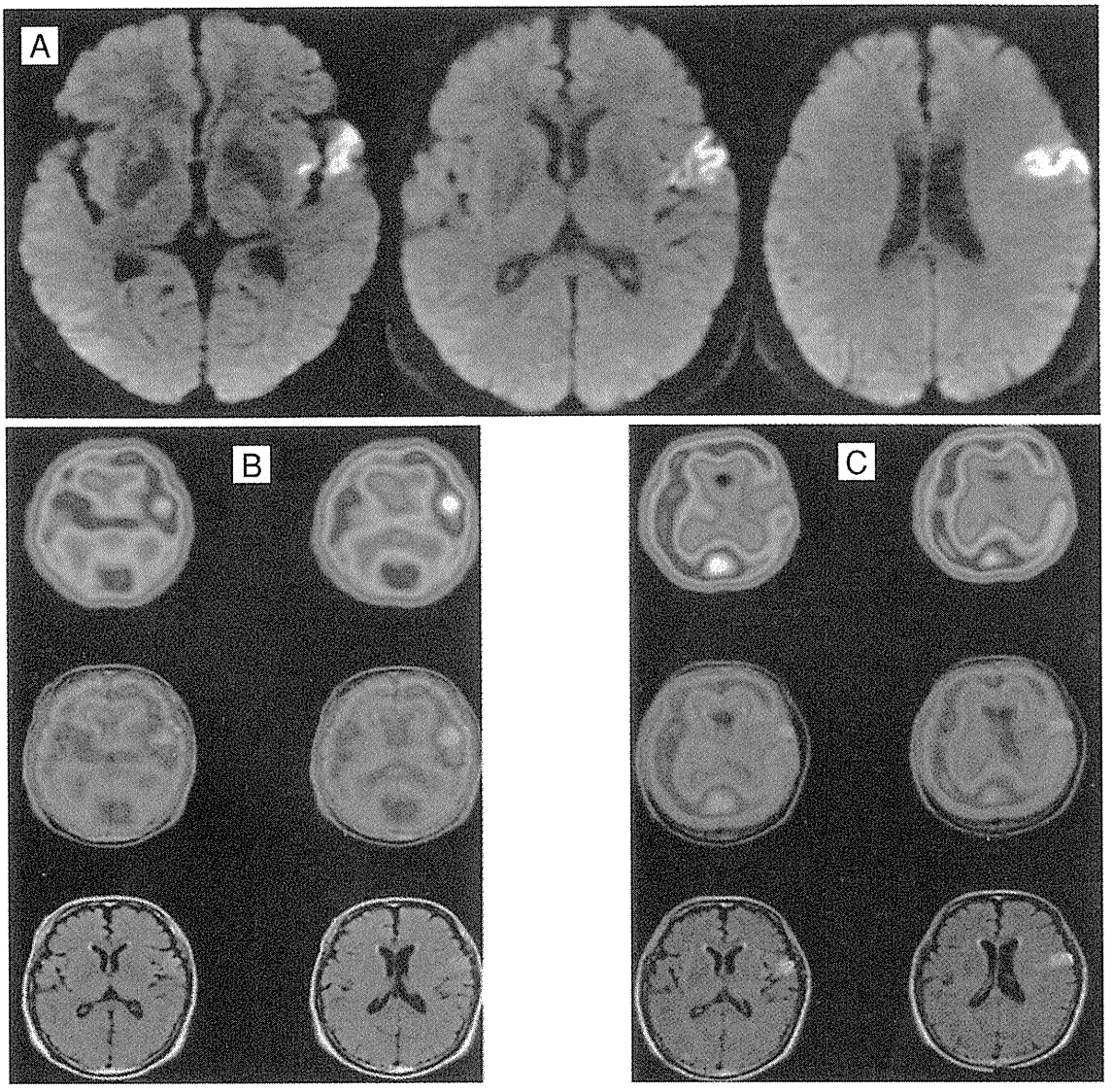

図1　入院時頭部MRIと^{123}I-IMP脳血流シンチグラフィー
A：入院時頭部MRI拡散強調像．左前頭葉中心前回，島皮質，側頭葉上側頭回に高信号域がみられた．B：^{123}I-IMP脳血流シンチグラフィー(発症5日目)．左前頭葉，側頭葉の梗塞部位に一致して血流増加を認めた．C：^{123}I-IMP脳血流シンチグラフィー(発症50日目)．梗塞部位に一致して血流は低下していた．

体は陰性であった．心電図は心房細動で，脳波は左前頭葉優位に6 Hzの徐波の混在があったが明らかなてんかん発作波はなかった．頸部血管エコーは正常．経食道心エコー検査で中等度の僧帽弁閉鎖不全，左心房拡大と，もやもやエコーを認めた．入院時の頭部MRI拡散強調画像では左前頭葉中心前回，島皮質，側頭葉上側頭回に高信号域がみられ(図1-A)，FLAIR画像でも同部位に高信号域を認めた．入院時の頭部MRAでは脳主幹動脈に狭窄・閉塞所見はなかった．発症5日目の^{123}I-IMP脳血流シンチグラフィーでは左前頭葉，側頭葉の梗塞部位に一致して血流増加を認めた(図1-B)．脳血流シンチグラフィー施行時に不随意運動はなかった．同日施行した脳血管造影検査では明らかな閉塞血管はなかった．

入院後経過：左中大動脈領域の心原性脳塞栓症と診断した．入院日からグリセオールとエダラボンの投与を行い，入院翌日の頭部CTで出血のないことを確認した上でヘパリンナトリウム10,000単位/日とワルファリンカリウム3 mg/日を開始した．意識障害，失語，眼球運動障害は翌日に改善した．舞踏アテトーゼ運動は自然経過で頻度が減少し，右下肢は発症10日目，右上肢は発症14日目に消失した．発症50日後の^{123}I-IMP脳血流シンチグラフィーは梗塞部位に一致して血流は低下していた(図1-C)．

考　察

脳梗塞急性期に舞踏アテトーゼ運動を呈した報告例[1)~3)]では，その責任病巣として基底核が多く，その運動調節機構(大脳皮質-線条体-淡蒼球-視床-大脳皮質に至る回路)が重要視されている．この回路は，基底核が大脳皮質から入力を受け，情報を処理し視床を介して大脳皮質に戻すことで四肢の運動を調整している[4)]．舞踏運動は，線条体から視床へ向かう抑制性出力が減弱することで視床から大脳皮質に至る興奮性出力が増大して生じると考えられている．大脳皮質および皮質下白質病変による舞踏運動は稀である[5)6)]．一方で，アテトーゼ運動は線条体，視床，中脳，淡蒼球などの病変で生じるとされる[7)]．

本例における舞踏アテトーゼ運動の発症機序は，左前頭葉中心前回，島皮質，側頭葉上側頭回が虚血に陥ったため，運動前野や体性感覚野から線条体や視床下核へ至る興奮性出力が遮断され，視床から大脳皮質への興奮性出力が増大した結果生じたと考えた．一方で，塞栓子が一時的に中大脳動脈水平部を閉塞し，線条体や淡蒼球が虚血に陥った影響も考えたが，経時的にMRI検査で評価したが同部位に梗塞巣は描出されなかった．

脳梗塞急性期に舞踏運動あるいは舞踏アテトーゼ運動を呈し，脳血流シンチグラフィーで検討した報告は少ない．報告例では梗塞部の血流が低下したとされるが[3)8)9)]，その撮影時期は急性期から慢性期と一定でない．Leeら[3)]は，顔面を含んだ左上下肢に片側舞踏アテトーゼ運動を生じ，急性期脳血流シンチグラフィーで右線条体と右後大脳動脈・中大脳動脈境界域の血流低下を認めた例を報告し，機序は右線条体の血流低下により片側舞踏アテトーゼ運動が生じたと考察した．本例においては，線条体の血流低下は認められなかった．大脳皮質の梗塞部位は慢性期に血流が低下しており，本例の舞踏アテトーゼ運動の責任病巣は線条体よりも大脳皮質病変を支持する結果であった．さらに大脳皮質の梗塞部位の血流が急性期に増加した理由は，早期再開通による過灌流によるものが考えられた．

われわれは，突然の片側舞踏アテトーゼ運動を呈し，DWIで対側前頭葉中心前回，島皮質，側頭葉上側頭回に病巣を認め，急性期の^{123}I-IMP脳血流シンチグラフィーで同部位の血流増加を認めた心原性脳塞栓症の1例を経験した．本例は視床から大脳皮質への興奮性出力の増加により片側舞踏アテトーゼ運動を生じた可能性があり，発症機序を考察する上で重要と考えられた．

まとめ

症例は58歳男性である．意識障害，失語，左側への共同偏視，右上下肢の舞踏アテトーゼ運動で発症した．心電図所見は心房細動を認めた．頭部MRI拡散強調画像で左前頭葉中心前回，島皮質，側頭葉上側頭回に高信号域を認め，心原性脳塞栓症と診断した．第5病日の^{123}I-IMP脳血流シンチグラフィーでは同部位の血流の上昇を認め，慢性期では同部位の血流は低下していた．本例は，片側舞踏アテトーゼ運動の発症機序を考察する上で貴重である．

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<Abstract>

Hemichoreoathetosis associated with cerebral cortex in cardioembolic infarction. A case report.

by
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We reported a case of cardioembolic stroke patient suffering hemichoreoathetosis due to the cerebral cortex lesions. A 58-year-old man with atrial fibrillation was admitted to our hospital with consciousness disturbance, aphasia, conjugate deviation of the eyes to the left, and left hemichoreoathetosis. Diffusion-weighted imaging disclosed hyper-intense lesions in the left precentral gyrus, superior temporal gyrus and insular cortex. Therefore, we made a diagnosis of cardioembolic stroke. On day 5 after admission, cerebral angiography demonstrated no specific lesion.

^{123}I-IMP brain single photon emission computed tomography showed increased cerebral blood flow in the left precentral gyrus, superior temporal gyrus and insular cortex. Therefore, on the basis of the above findings, the hemichoreoathetosis was caused by increased excitability to the cerebral cortex from thalamus.

* * *

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IV t-PA therapy in acute stroke patients with atrial fibrillation

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ABSTRACT

Background and purpose: Atrial fibrillation (AF) is a predictor for severe stroke. Intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes in patients with acute ischemic stroke. We investigated clinical characteristics and patient outcome in patients with and without AF after t-PA therapy.
Methods: Consecutive ischemic stroke patients treated with t-PA within 3 h of stroke onset were studied prospectively. MRI examinations, including diffusion weighted imaging and MRA, were performed before t-PA thrombolysis. NIHSS scores were obtained before and 7 days after t-PA infusion. The patients were divided into two groups (AF group and Non-AF group). Their clinical characteristics and outcome 7 days and 3 months after t-PA therapy were compared.
Results: 85 patients (56 males, mean age, 73.4±11.5 years) were enrolled in the present study. The AF-group had 44 patients, and the Non-AF group had 41 patients. Fewer patients with AF had dramatic improvement at 7 days and favorable outcome (mRS 0–1) at 3 months after t-PA therapy than patients without AF (31.8% vs. 61.0%, $P=0.007$, and 15.9% vs. 46.3%, $P=0.002$). On the other hand, worsening at 7 days and poor outcome (mRS>3 and death) at 3 months after t-PA therapy were more frequently observed in AF group than Non-AF group (22.7% vs. 9.8%, $P=0.107$, and 70.5% vs. 41.5%, $P=0.007$). After adjusting age and gender, patients with AF more frequently had worsening and poor outcome than those without AF (adjusted OR; 4.54, 95% CI 1.04–19.75, $P=0.044$, and adjusted OR; 2.8, 95% CI 1.10–7.28, $P=0.032$).
Conclusion: The present study found that acute ischemic stroke patients with AF more frequently had poor outcome after IV-t-PA therapy compared with those without AF.

1. Introduction

We previously reported that atrial fibrillation (AF) was observed in 21.1% of 15,831 acute ischemic stroke patients in the J-MUSIC study [1] and that AF was a predictive factor for severe stroke and early death [2]. Therefore, attention needs to be paid to the treatment of acute stroke patients with AF in order to improve patients' outcomes. Intravenous administration of tissue plasminogen activator (t-PA) can improve clinical outcomes in patients with acute ischemic stroke [3,4]. Early arterial recanalization has been recognized as a marker of a good outcome after t-PA infusion [5–10]. Using transcranial Doppler (TCD) examination Alexandrov et al. [11] reported that, during t-PA infusion, recanalization was complete in 30% and partial in 40% of patients. Recently, we reported that AF was independently associated with a lack of early recanalization after t-PA administration [12]. Furthermore, using the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial, [3] subanalysis reveled that AF was associated with poor outcome after t-PA therapy [13]. Brown et al. reported that AF was not related with major neurological improvement within 24 h after t-PA infusion [14]. Therefore, we hypothesized that acute stroke patients with AF were less likely to respond to t-PA therapy compared with those without AF. We investigated clinical characteristics and patient outcome after t-PA therapy in acute stroke patients with and without AF.

2. Subjects and methods

Consecutive patients with acute ischemic stroke treated with t-PA within 3 h of stroke onset between October 2005 and August 2008 were studied prospectively. Patients with heart valve replacements, pacemakers, or cranial artery clipping were excluded, since MRI is contraindicated in these patients.

The following clinical data were collected from all patients: 1) patient age and gender; 2) arterial blood pressure before t-PA infusion; 3) NIHSS score before and 7 days after t-PA infusion; 4) the presence of arterial occlusion on MRA prior to t-PA infusion; 5) vascular risk factors, including hypertension (HT), hyperlipidemia (HL), and diabetes mellitus (DM); 6) the presence of potential cardiac sources of emboli, including AF, 7) laboratory parameters prior to t-PA infusion; and 8) modified Rankin scale (mRS) at 3 months after t-PA therapy. The inclusion and exclusion criteria for the use of intravenous t-PA were the same as those used in the Japan Alteplase Clinical Trial [15].

Prior to t-PA infusion, magnetic resonance imaging (MRI) studies, including DWI and MRA, were performed to identify the occluded

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arteries. The presence of large artery occlusion was determined on MRA. Occluded arteries on the initial MRA were identified as follows: M1 occlusion, M2 occlusion, posterior cerebral artery (PCA), internal cerebral artery (ICA), vertebral artery (VA), and basilar artery (BA) occlusion. The experienced researcher (K.K.) who evaluated the MRA findings was blinded to the patients' clinical backgrounds. MRI was performed using a commercially available echo planar instrument operating on a 1.5-T unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI, USA). The imaging protocol consisted of a diffusion-weighted echo planar (TR/TE=8000/70 ms) imaging series and intracranial MR angiography.

Seven days after t-PA therapy, four levels of clinical recovery, based on modified methods used in previous studies, were used [3,16]. Dramatic improvement was defined as a 10-point reduction in the total NIHSS score or a total NIHSS score of 0 or 1. Good improvement was defined as a 4-point reduction in the total NIHSS score. No change was defined as from 3-points increase to 3-points reduction in the total NIHSS score. Worsening was defined as a 4-point increase in the total NIHSS score. Symptomatic cerebral hemorrhage was defined as an increase in the total NIHSS score of 4 when the ICH was the likely cause of the clinical deterioration. Favorable and poor outcome at 3 months after t-PA therapy were defined as a mRS 0–1 and >3 or death, respectively.

We divided the patients into two groups; AF group had AF and Non-AF group did not have AF. The groups' clinical characteristics were compared. The significance of inter-group differences was assessed using the chi-square test for categorical variables and the Mann–Whitney *U* test and the Kruskal–Wallis *U* test for continuous variables. After adjusting age and gender, we calculated adjusted OR to investigate the effect of AF on patient outcome. Values of $P<0.05$ were considered statistically significant. Statistical analysis was performed using StatView version 5 statistical software. All study protocols followed the principles outlined in the Declaration of Helsinki, and informed consent was obtained from all patients.

Table 1
Characteristics of patients with and without AF

	Patients with AF	Patients without AF	*P*
	n=44	*n*=41	
Age	77.2±9.0	69.4±12.5	0.0062
Male	27(61.4%)	29(70.7%)	0.3627
Hypertension	28(63.6%)	21(51.2%)	0.2470
Diabetes mellitus	8(18.2%)	9(22.0%)	0.6642
Hyperlipidemia	6(13.6%)	13(31.7%)	0.0457
Baseline NIHSS score	17.3±6.5	12.3±7.5	0.0010
≤10	8(18.2%)	20(48.8%)	0.0027
MRA before t-PA infusion			
Presence of occluded artery	40(90.8%)	22(53.7%)	<0.0001
ICA occlusion	11(25.0%)	8(19.5%)	
M1 occlusion	20(45.5%)	6(14.6%)	
M2 occlusion	6(13.6%)	4(9.8%)	
PCA occlusion	1(2.3%)	0	
BA occlusion	2(4.5%)	3(7.3%)	
VA occlusion	0	1(2.5%)	
No occlusion	4(9.1%)	19(46.3%)	
Systolic blood pressure (mm Hg)	158.1±21.2	156.3±24.0	0.3850
Diastolic blood pressure (mm Hg)	84.9±17.5	86.2±17.4	0.8746
Time from symptom onset to treatment, min	148.3±27.8	147.6±24.8	0.7237
HbA1C (%)	5.6±0.6	5.7±0.8	0.8897
Total-cholesterol (mg/dl)	187.6±41.4	201.1±37.1	0.0764
CRP (mg/dl)	0.5±1.3	00.7±2.3	0.4990
Leucocytes (/μl)	6398.7±2055.6	6687.8±2657.8	0.6411
Erythrocytes (×10,000/μl)	418.4±61.7	435.9±55.7	0.3650
Platelets (×10,000/μl)	18.7±5.3	20.5±4.6	0.0246
Albumin (g/dl)	3.7±0.4	4.0±0.4	0.1281
GOT (IU/l)	23.2±25.8	23.0±16.3	0.3581
GPT (IU/l)	27.7±25.7	26.1±12.7	0.4674
Creatinine (mg/dl)	0.96±0.87	0.77±0.24	0.1871
Sodium (Na) (mEq/l)	139.8±2.8	140.2±3.5	0.4034
Potassium (K) (mEq/l)	4.0±0.4	4.0±0.5	0.8916
Glucose (mg/dl)	152.8±48.1	139.1±38.7	0.1555
Fibrinogen (mg/dl)	302.9±88.1	288.6±84.1	0.3139

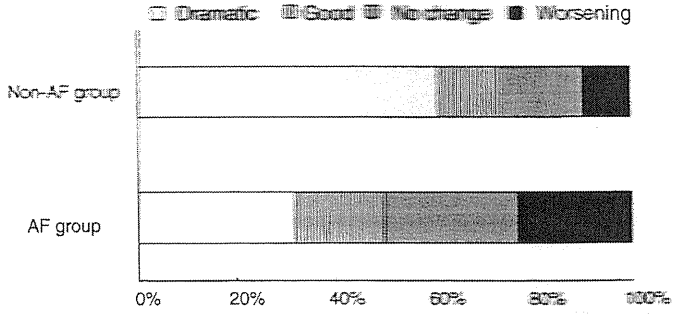

Fig. 1. Neurological recovery of patients with and without AF at 7 days after t-PA therapy.

3. Results

A total of 86 consecutive stroke patients were treated with t-PA. One patient was excluded because of having a pacemaker. Thus, 85 patients (56 males, 29 females; mean age, 73.4±11.5 years) were enrolled in the present study. The time from symptom onset to the initial MRI study was 93.6±31.3 min, and the time from symptom onset to the t-PA bolus was 148.0±26.2 min. The baseline NIHSS score was 14.9±7.4.

44 (51.8%) patients (AF group) had AF and 41 (48.2%) patients (Non-AF group) did not have one. One patient with AF had a symptomatic cerebral hemorrhage within 24 h of t-PA infusion. Table 1 shows the characteristics of the AF and Non-AF groups. Hyperlipidemia was less common in the AF group than in the Non-AF group (13.6% vs. 31.7%, $P=0.0457$). The baseline NIHSS score was higher in the AF group (17.3±6.5) than in the Non-AF group (12.3±7.5, $P=0.0010$). M1 occlusion was more frequent in the AF group (45.5%) than in the Non-AF group (14.6%, $P=0.0254$), and no occlusion was more common in the Non-AF group (46.3%) than in the AF group (9.1%, $P=0.0024$). Platelets was lower in the AF group than in the Non-AF group (18.7±5.3 ×10,000/μl vs. 20.5±4.6 ×10,000/μl, $P=0.0246$). There were no significant differences between the two groups in other clinical factors.

On day 7, NIHSS score was higher in AF group (14.2±10.5) than in Non-AF group (7.3±11.4, $P=0.0001$). 39 patients had dramatic improvement, 13 patients had good improvement, 19 patients had no change, and 14 patients had worsening. Fewer patients with AF had dramatic improvement than patients without AF (31.8% vs. 61.0%, $P=0.007$). On the other hand, worsening was more frequently observed in AF group than Non-AF group (22.7% vs. 9.8%, $P=0.107$) (Fig. 1). After adjusting age and gender, patients with AF more frequently had worsening than those without AF (adjusted OR; 4.54, 95% CI 1.04–19.75, $P=0.044$), and

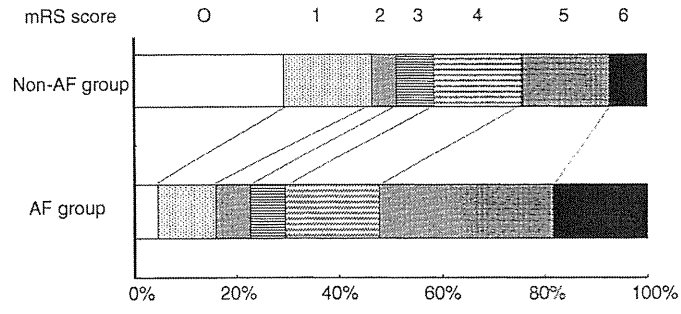

Fig. 2. Modified Rankin scale of patients with and without AF at 3 months after t-PA therapy. The scores on modified Rankin scale indicate the following, 0, no symptom at all; 1, no significant disability despite symptom; 2, slightly disability; 3moderate disability; 4, moderately severe disability; 5, severe disability; 6, death.

patients without AF more frequently had dramatic improvement than those with AF (adjusted OR; 3.33, 95% CI 1.28–8.66, $P=0.014$).

At 3 months after t-PA therapy, 26 patients had favorable outcome, and, 48 patients had poor outcome. Fewer patients with AF had favorable outcome than patients without AF (15.9% vs. 46.3%, $P=0.002$). On the other hand, poor outcome was more frequently observed in AF group than Non-AF group (70.5% vs. 41.5%, $P=0.007$) (Fig. 2). After adjusting age, and gender, patients with AF more frequently had poor outcome than those without AF (adjusted OR; 2.8, 95% CI 1.10–7.28, $P=0.032$), and patients without AF more frequently had favorable outcome than those with AF (adjusted OR; 3.9, 95% CI 1.35–11.31, $P=0.012$).

4. Discussion

The present study found that acute ischemic stroke patients with AF more frequently had poor outcome after IV-t-PA therapy compared with those without AF. Early arterial recanalization has been recognized as a marker of good outcome after t-PA infusion [5–10]. Molina et al. [8] reported that early recanalization was more frequent in patients with cardioembolic stroke than with other stroke types. They reported that 59% of cardioembolic strokes displayed recanalization. However, they did not analyze the relationship between AF and the presence of early recanalization. We previously reported that AF was an independent factor associated with lack of recanalization after t-PA administration [12]. We suggested the following reason to explain this finding. Clot dissolution depends on clot size, site of occlusion, clot composition, the surface area of the clot exposed to blood flow, and penetration of t-PA into the clot structure [5]. Fresh and old clots form in cardiac cavities, including the left atrium, in cases with AF [17]. Furthermore, TEE sometimes demonstrates large thrombi in the left atrium in stroke patients with AF. Old and large thrombi may be more resistant to thrombolysis than fresh and small thrombi. Therefore, patients with AF appear to be more likely to have large or old thrombi, which are resistant to t-PA therapy compared with those without AF.

AF was associated with an increased risk of death in the first four weeks after stroke [18]. Strokes in patients with AF may chiefly be cardioembolic, which causes a sudden occlusion of large cerebral arteries without sufficient collateral blood flow, results in more severe strokes [19,20]. In the present study, baseline NIHSS was significantly higher in AF group than in Non-AF group. Several investigators have reported that ICA occlusion was not likely to respond to t-PA and that patients' with ICA occlusion had poor outcomes [21–23]. Our data showed that there was no difference in frequency of ICA occlusion between patients with and without AF. However, patients with AF had more frequently occluded artery on initial MRA than those without AF. Therefore, patients with AF are likely to have more worsening and poor outcome.

The present study had several limitations. First, we did not always evaluate the heart diseases using transesophageal echocardiography (TEE) and transthoratic echocardiography (TTE) in detail. Tomita et al. [24]. reported that 77% of 2677 patients with AF had heart diseases, such as hypertensive heart disease, ischemic heart diseases, valvular heart diseases, sick sinus syndrome, and cardiomyopathy. Second, the rates of recanalization may have been lower because the dose of t-PA (0.6 mg/kg in Japan) [15] is lower than the internationally approved dosage of 0.9 mg/kg. Third, the use of MRA is somewhat inaccurate for detection of vessel occlusion or stenosis [25]. Finally, the number of our patients was small, so, we need a large sample to prove our hypnosis.

In conclusion, acute ischemic stroke patients with AF more frequently had poor outcome after IV-t-PA therapy compared with those without AF.

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