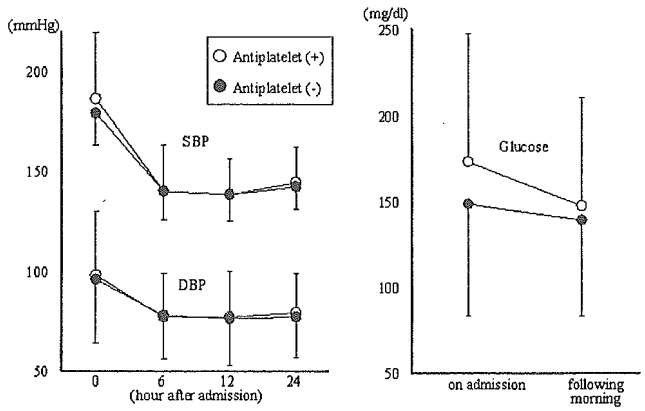

Figure. Changes in systolic (SBP) and diastolic blood pressure (DBP) and blood glucose between patients with (open circle) and without antiplatelet therapy (closed circle). Two-way repeated-measures analysis of variance (ANOVA) shows a group × time interaction for blood glucose ($p < 0.02$), not for SBP or DBP. One-way repeated-measures ANOVA shows a decrease in SBP and DBP in both groups ($p < 0.0001$). Paired t test shows a decrease in blood glucose in both groups ($p < 0.001$). Patients who died within 24 hours after admission were excluded because of the lack of 24-hour follow-up measurements.

(median 8.4 mL), was assessed for only 180 patients, because the remaining 71 died emergently or were treated by surgical evacuation. Hematoma enlargement was more common in patients who received antiplatelets ($p < 0.005$).

The NIHSS score at admission for patients receiving antiplatelets was 6 or lower in 22 patients, between 7 and 15 in 13 patients, and 16 or greater in 22 patients. For the patients not receiving antiplatelets, the NIHSS score at admission was 6 or lower in 71 patients, between 7 and 15 in 67 patients, and 16 or greater in 56 patients. Emergent surgical evacuation was more frequently needed in patients receiving antiplatelets ($p < 0.02$). Fourteen patients died within 24 hours after admission, for whom we did not perform surgical therapy because of severe thrombocytopenia due to end-stage leukemia in 1 patient with subcortical hemorrhage, severe brainstem dysfunction and coma in 6 patients with pontine hemorrhage, and refusal of surgical evacuation by the family in the remaining 7 comatose patients with putaminal or subcortical hemorrhage. For these 14 patients, we did not use hypertensive drugs or mechanical ventilation. More than half (58%) of the patients receiving antiplatelets emergently died or were treated by surgical evacuation or showed hematoma enlargement, vs 30% of patients who were not receiving antiplatelets ($p < 0.0005$). This percentage amounted to 58% (18 of 31 patients) for the patients taking 81 to 100 mg aspirin, the most prevalent antiplatelet agent and dosage in this study, and 56% (5 of 9) for the patients taking multiple antiplatelet agents.

Of the baseline clinical characteristics, physiologic status at admission, CT findings, and neurologic status, the 11 items in table E-2, A, were significantly or marginally significantly correlated with hematoma volume on CT1 greater than 25 mL using the χ^2 test. After multivariate analysis, heart disease, liver disease, glucose greater than 200 mg/dL, putaminal hemorrhage, subcortical hemorrhage, ventricular bleeding, interval between onset and CT1 less than 3 hours, and NIHSS score at admission of 16 or greater were independently related to the large hematoma. Similarly, SBP greater than 200 mmHg, pontine hemorrhage, ventricular bleeding, hematoma volume on CT1 greater than 25 mL, and mRS score before ICH of 3 or greater were independently related to NIHSS score at admission of 16 or greater (see table E-2, B). Antiplatelet therapy was not an independent predictor for these two indicators.

Using the χ^2 test, the items listed in table 2 (more detailed data are provided in table E-3) were significantly or marginally significantly correlated with the three indicators for acute deterioration of ICH. After multivariate analysis, antiplatelet therapy was independently predictive of hematoma enlargement together with platelet count less than 100,000/μL and interval between onset and CT1 less than 3 hours (see tables 2 and E-3, A). Similarly, antiplatelet therapy was independently predictive of emergent surgical evacuation together with putaminal hemorrhage and hematoma volume on CT1 greater than 25 mL (see tables 2 and E-3, B). Platelet count less than 100,000/μL and pontine hemorrhage were independently predictive of emergent death (see tables 2 and E-3, C). Multivariate analysis using 31 patients taking 81 to 100 mg aspirin and 194 patients not taking antiplatelets as subjects indicated that aspirin therapy was also independently predictive of hematoma enlargement (odds ratio [OR] 5.81, 95% CI 1.01 to 33.3) and emergent surgical evacuation (OR 5.07, 95% CI 1.48 to 17.4).

We determined the predictors for any of hematoma enlargement, emergent evacuation, or emergent death (see tables 2 and E-3, D). Antiplatelet therapy was an independent predictor for any of the above three indicators and increased 7.5-fold the risk of the occurrence of any of these three indicators. Platelet count less than 100,000/μL, putaminal hemorrhage, ventricular bleeding, hematoma volume on CT1 greater than 25 mL, interval between onset and CT1 less than 3 hours, and NIHSS score at admission of 16 or greater were other independent predictors. After multivariate analysis using 31 patients taking 81 to 100 mg aspirin and 194 patients not taking antiplatelets as subjects, aspirin therapy was also independently predictive of any of the above three indicators (OR 5.02, 95% CI 1.42 to 17.7).

Finally, we determined changes in SBP, DBP, and blood glucose among patients with and without hematoma enlargement and with emergent evacuation (figure E-1). In any groups, these variables became toward normal ranges in the follow-up measurements.

Discussion. We sought to clarify the negative effect of antiplatelet therapy on the acute clinical outcome of ICH. First, patients with ICH taking antiplatelet therapy were older and more frequently had symptomatic ischemic stroke, diabetes mellitus, and heart disease than those not taking antiplatelet therapy. Second, antiplatelet therapy was not predictive of a larger hematoma or more severe neurologic deficits at admission, both of which are indicators of the initial ICH severity. Third, antiplatelet therapy was an independent predictor for acute hematoma enlargement and emergently undergoing hematoma

Table 2 Multivariate analysis of independent predictors for acute deterioration of ICH

Item	*p* Value	OR (95% CI)
Hematoma enlargement (increase in volume >40% between two CTs)*		
Antiplatelet therapy	<0.01	7.67 (1.62–36.4)
Platelets <100,000/μL	0.024	37.8 (1.59–899.2)
ICH onset to CT1 <3 h	<0.005	8.59 (2.01–36.8)
Emergent surgical evacuation of hematoma†		
Antiplatelet therapy	0.021	3.10 (1.18–8.15)
Putaminal hemorrhage	<0.001	4.90 (1.89–12.7)
Volume on CT1 >25 mL	<0.0001	32.0 (10.7–95.4)
Emergent death‡		
Platelets <100,000/μL	0.038	19.8 (1.18–330.2)
Pontine hemorrhage	0.015	17.1 (1.74–168.4)
Any of hematoma enlargement, emergent evacuation, or emergent death§		
Antiplatelet therapy	<0.0005	7.45 (2.46–22.5)
Platelets <100,000/μL	<0.005	51.0 (3.91–666.6)
Putaminal hemorrhage	<0.0005	5.77 (2.15–15.5)
Ventricular bleeding	<0.01	3.50 (1.35–9.03)
Volume on CT1 >25 mL	<0.0001	11.0 (4.36–27.6)
ICH onset to CT1 <3 h	<0.005	3.94 (1.66–9.36)
NIHSS score at admission ≥16	0.030	2.85 (1.11–7.34)

* Symptomatic ischemic stroke, total cholesterol <130 mg/dL, fibrinogen <200 mg/dL, ventricular bleeding, volume on CT1 >25 mL, and National Institutes of Health stroke scale (NIHSS) score at admission ≥16 were significantly or marginally significantly correlated by χ^2 test but were not independently correlated after multivariate analysis.

† Liver disease, neoplasm, diastolic blood pressure >110 mm Hg, glucose >200 mg/dL, ventricular bleeding, intracerebral hemorrhage (ICH) onset to CT1 <3 hours, and NIHSS score at admission ≥16 were not independently correlated after multivariate analysis.

‡ Symptomatic ischemic stroke, systolic blood pressure >200 mm Hg, glucose >200 mg/dL, volume on CT1 >25 mL, ventricular bleeding, and NIHSS score at admission ≥16 were not independently correlated after multivariate analysis.

§ Symptomatic ischemic stroke, diabetes mellitus, liver disease, neoplasm, systolic blood pressure >200 mm Hg, and glucose >200 mg/dL were not independently correlated after multivariate analysis.

OR = odds ratio.

evacuation, as well as for the occurrence of acute hematoma enlargement, emergent death, or emergent hematoma evacuation, which indicate acute ICH deterioration within the first 2 days.

As clinical factors to affect ICH outcome, anticoagulation, hematoma size, patient age, level of consciousness, hypertension, diabetes, admission to a neurologic intensive care unit, and location within the brainstem were reported.[3] Clinical and biologic markers of the inflammatory reaction have recently been reported to be predictive of early neurologic deterioration in ICH patients.[15] However, antiplatelets have not up to now been shown to affect ICH outcome. One reason why antiplatelet-related ICH has been understudied may be the low percentage of patients with ICH receiving antiplatelet therapy. For example, a study performed within the past decade reported that less than 5% of patients with ICH were taking antiplatelets.[12] A recent study reported that 30% of the patients with ICH were taking antiplatelets.[3] During the past few years, the use of antiplatelets has become prevalent because oral antiplatelets have proven protective in high-vascular-risk patients, including those with acute and chronic stroke.[16,17] Consequently, the association of antiplatelet therapy with the initial severity and clinical outcome of ICH has become a central issue.

Although active bleeding of ICH is generally thought to cease within the first few hours, several studies reported that between 14% and 38% of patients show hematoma enlargement on the second-day follow-up CT.[12-14,18,19] Long-term antiplatelet therapy suppresses platelet function and seems to enhance active bleeding in the hyperacute stage occurring after the initial CT is performed. In the current study, the frequency of hematoma enlargement was not high even for patients receiving antiplatelet therapy (24%). An explanation for the low frequency of hematoma enlargement may be the exclusion from the analysis of many patients with potential hematoma enlargement because of emergent death or surgery. A severe mass effect often causes emergent death and surgery, and the mass effect seems to be associated with a large hematoma at admission, hematoma enlargement after admission, and secondary edema formation. An acute mass effect occurring

within 2 days was reported to be associated with hematoma enlargement, whereas a later mass effect was reported to be associated with an increase in edema.[20]

In table 2 (table E-3, D), we identify the seven independent predictors for acute ICH deterioration. Among them, antiplatelet therapy and a low platelet level might alter platelet function and consequently prolong active bleeding. Putaminal hemorrhage and large hematoma at admission might reflect a severe mass effect and consequent emergent death or surgery. The relationship between hematoma enlargement and initial hematoma size has been disputed.[12,14,18] Ventricular bleeding might cause hydrocephalus and worsen patient outcome. An early visit after onset seems to increase the opportunity for continuous active bleeding after the initial CT. In addition, patients with severe initial symptoms seem to visit hospital emergency departments often, although an early visit after onset was not predictive of severe neurologic deficits in this study. In the current analysis, various comorbidities including previous cerebrovascular and cardiovascular disease and risk factors for arteriosclerosis were not independent predictors for acute ICH deterioration except for thrombocytopenia.

Insufficient control of physiologic variables in the hyperacute stage, as well as their initial severity, could have affected the risk of hematoma expansion and clinical deterioration. We principally decreased SBP to below 150 mm Hg in acute ICH patients, which seems to be optimal in preventing hematoma growth,[14] and similarly decreased blood glucose toward the reference range (see figures 1 and E-1). Thus, differential control of these variables did not seem to essentially cause difference in the acute outcome in our patients.

The results of the current study warn about the risk of ICH deterioration in patients receiving antiplatelet therapy and suggest that the next logical step would be to determine the relative importance in relation to ICH deterioration of antiplatelet agent dosage and the use of multiple antiplatelets. These issues were not fully examined in this study because of the small number of patients enrolled. In addition, a few patients took an excess dosage of antiplatelets compared with the recommended dosage in Japan (e.g., 300 mg ticlopidine), and it might affect generalization of the current results. The current results showed that 81 to 100 mg aspirin, the most prevalent antiplatelet agent and dosage in this study, was independently predictive of acute ICH deterioration within the first 2 days. Prospective trials using large populations with antiplatelets are needed to overcome these limitations and clarify unresolved issues in this study, including outcome of ICH according to antiplatelet agent and dosage.

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Serial Transoral Carotid Ultrasonographic Findings in Extracranial Internal Carotid Artery Dissection

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Extracranial internal carotid artery dissection (EICAD) is a recognized cause of ischemic stroke, including transient ischemic attack (TIA). However, therapeutic strategies remain controversial. A previous study emphasized that completed stroke usually occurs in the first few days after onset of the first symptoms in EICAD,[1] so early diagnosis is necessary to plan future therapeutic trials. We report a case of TIA detected clearly on transoral carotid ultrasonography (TOCU) in early-stage EICAD.

Case Report

A 52-year-old man was admitted to our hospital with a 4-day history of multiple episodes of transient left hemiparesis and dysarthria. He had a 10-year history of hypertension but no history of smoking or previous cervical or cranial trauma. Family history included subarachnoid hemorrhage in an uncle. On admission, general physical examinations revealed hypertension (178/78 mm Hg) and obesity (body mass index, 29.4) but no other abnormalities such as carotid bruits. Neurologic examinations confirmed Horner syndrome (ptosis and miosis) on the right side, which disappeared by hospital day 3. No symptoms of headache or neck pain were reported.

The results of the laboratory examinations were normal, including levels of α_1-antitrypsin. Xanthochromia was not seen in cerebrospinal fluid. Brain diffusion-weighted imaging on day 1 revealed acute cortical and subcortical infarction in the right middle cerebral artery territory. Conventional carotid ultrasonography on day 1 showed no atherosclerotic changes in the bilateral carotid arteries. However, we detected a high-resistance flow pattern, indicating the presence of distal internal

Abbreviations
EICAD, extracranial internal carotid artery dissection; ICA, internal carotid artery; TOCU, transoral carotid ultrasonography

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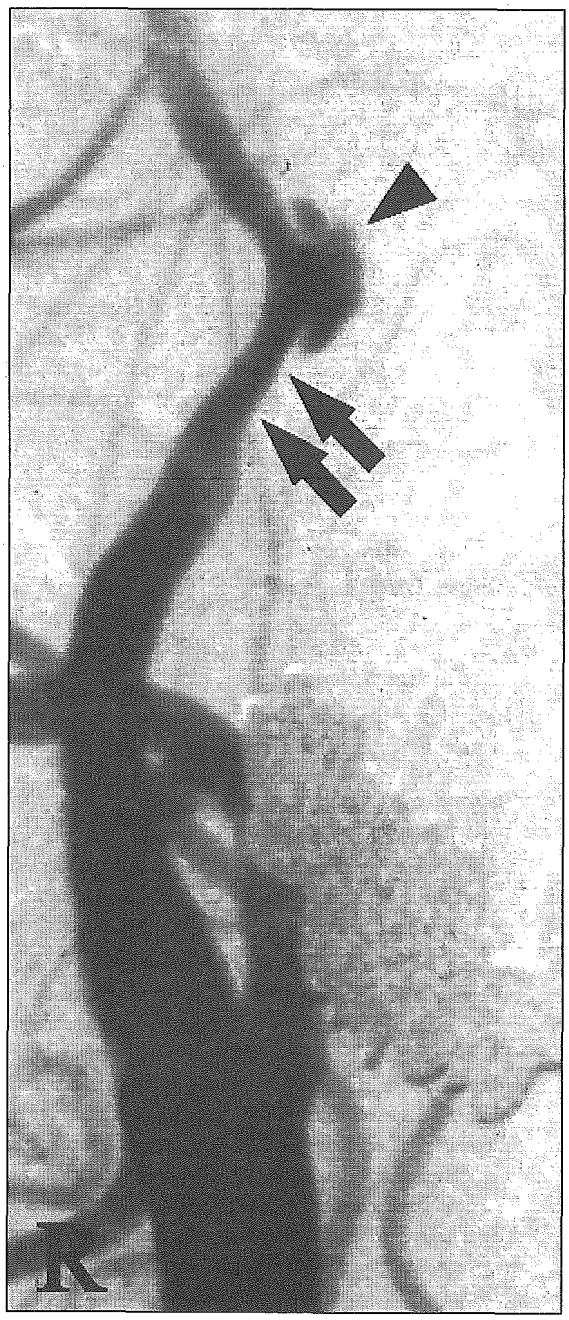
carotid artery (ICA) stenosis or occlusion. Cerebral angiography performed on hospital day 1 revealed luminal irregularity, mild stenosis, and outpouching of the right ICA at the C1 vertebral level (Figure 1). Renal arteriography performed after cerebral angiography showed no abnormalities.

Figure 1. Frontal view of the right common carotid arteriography on day 1 shows luminal irregular scalloping (arrows) and outpouching of the distal ICA (arrowhead). R indicates right side of image.

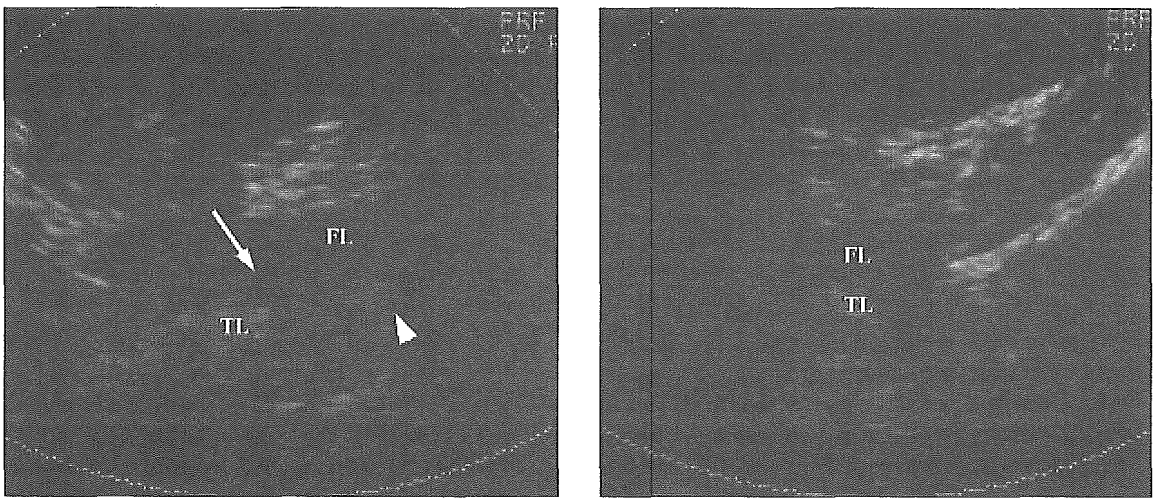


After informed consent was obtained from the patient, TOCU was performed 20 hours after admission. An ATL Ultramark 9 color Doppler flow imaging system (Philips Medical Systems, Bothell, WA) equipped with a 9- to 5-MHz convex array transducer (C9-5 ICT) was used for TOCU in accordance with previously described methods.[2] This transducer was originally designed for transrectal use. We prepared a new transducer for exclusive use for TOCU. The probe tip was painted with echo jelly and was covered with a clean cover and gently touched to the pharyngeal posterolateral wall. In the right ICA, a dilated lumen was seen (diameters, 7.9 mm [right] and 4.0 mm [left]), and a septum wall was seen separating a lumen with blood flow from an eccentric lumen without blood flow (false lumen) (Figure 2A). At the narrowing of the true lumen (Figure 2, A and B), a severe stenotic flow pattern (peak systolic flow velocity, 300 cm/s [right] and 120 cm/s [left]) was apparent. All these findings supported a diagnosis of TIA caused by right spontaneous EICAD.

Anticoagulant (argatroban) and antiplatelet (aspirin) therapies were administered for 1 week, and antiplatelet therapy was continued. Observation studies using TOCU were performed at the bedside on day 15 and revealed recovery in the size of the true lumen and increasing echogenicity of the false lumen (Figure 3, A and B). Peak systolic flow velocity in the right ICA decreased to 120 cm/s, which was similar to the value of the left ICA. Transoral carotid ultrasonographic findings, which were performed once a month at our outpatient clinic during 10 months of follow-up, had no changes except for increasing echogenicity of the false lumen. The patient had neither ischemic events nor iatrogenic adverse effects.

Discussion

Extracranial internal carotid artery dissection is estimated to be involved in about 2.5% of all first ischemic strokes and 10% to 20% of ischemic strokes in young adults, and it occurs below the C1–2 vertebral level in a substantial number of patients.[3] The mechanism of cerebral ischemia in patients with EICAD is suggested to be predominantly thromboembolic,[4] so antithrombotic drugs may be effective in EICAD. However, to our knowledge, no randomized trials comparing either anticoagulant or antiplatelet therapies



A B

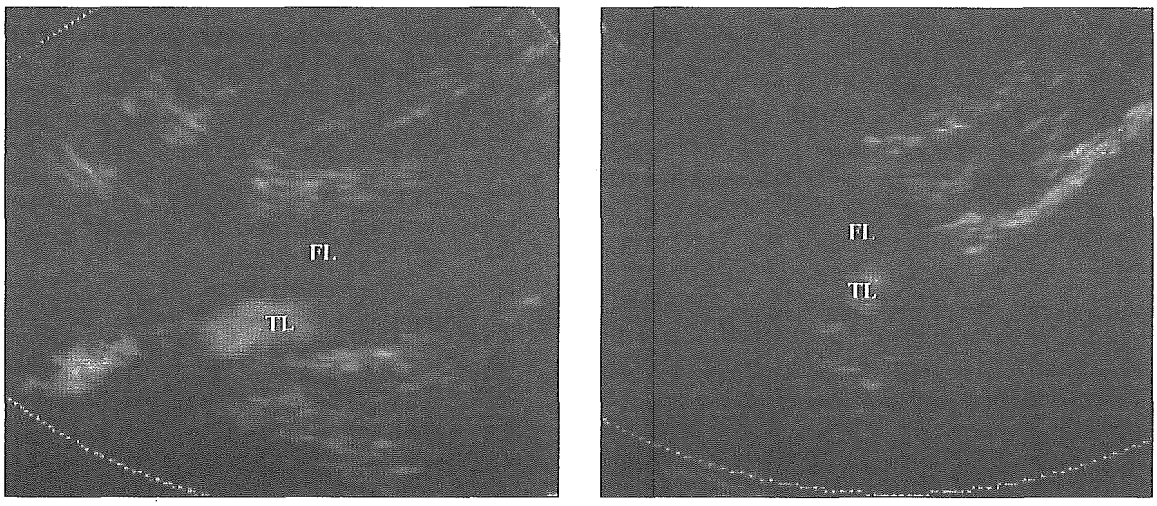
Figure 2. Color Doppler studies of the right distal ICA by TOCU on day 2. **A**, Longitudinal view shows a septum (arrow) separating the true lumen from a false lumen and narrowing of the true lumen (arrowhead). **B**, Short axial view at the narrowing of the true lumen also shows the true and false lumens. FL indicates false lumen; and TL, true lumen.

with controls have been undertaken.[5] Biousse et al[1] found that completed stroke usually occurs in EICAD within the first few days after onset of the first symptoms. They emphasized that any potential preventive treatment should be initiated as soon as possible after the first onset of symptoms. Early diagnosis of EICAD is thus necessary. Our case of recurrent TIA in spontaneous EICAD was diagnosed early on the basis of TOCU.

Although noninvasive studies have been developed to detect EICAD, the standard examination remains conventional angiography. However, typical angiographic signs are often difficult to recognize in patients with small changes in the lumen because conventional angiography cannot assess a false lumen filled with agglutinative thrombus. Furthermore, recent studies have needed 7 to 8 days from onset to diagnosis confirmed by conventional angiography.[6,7] In our

Figure 3. Color Doppler studies of the right distal ICA by TOCU on day 15. **A**, Longitudinal view. **B**, Axial view reveals dilatation of the true lumen and increasing echo intensity of the false lumen. FL indicates false lumen; and TL, true lumen.

A B



case, despite the absence of headache or neck pain, the false lumen, which could not be detected on conventional carotid ultrasonography, identified on TOCU allowed positive diagnosis of EICAD within 24 hours of admission (4 days after onset). According to imaging studies in the early stage of this case, we consider that in a patient with a presumptive clinical diagnosis of ICA dissection in whom the conventional carotid ultrasonographic findings are negative, TOCU should be performed before invasive angiographic imaging, either intravenous or intra-arterial.

After the diagnosis was established, serial improvements in EICAD were noninvasively observed at the bedside in this case. Dissection represents a dynamic disease, so noninvasive follow-up evaluations of the affected artery are important to confirm the diagnosis and allow informed therapeutic decision making. Although recent developments in imaging devices such as computed tomography and magnetic resonance imaging have enabled noninvasive observation of EICAD, these techniques are rather expensive for repeated follow-up studies. Conventional carotid ultrasonographic assessment may also prove useful for economical evaluation of EICAD. However, most spontaneous EICADs involve the distal extracranial segments of the ICA before the petrous portion, so conventional carotid ultrasonography is unable to provide direct imaging evidence of dissection because of obstruction by the mandibular bone. Conversely, TOCU can directly, repetitively, and economically visualize dissection in distal extracranial ICA segments. We previously reported TOCU findings in the EICAD, but they were evaluated only 1 month after the stroke onset.[8] To our knowledge, this is the first report showing serial findings of acute EICAD evaluated by TOCU.

Although TOCU allows quick and noninvasive follow-up at the bedside, it should be kept in mind that there is a limit of the observation range in TOCU. Usually, the distal extracranial ICA can be visualized as a vertical linear vessel with an approximate length of 3 cm, and the carotid bifurcation cannot be visualized by TOCU.[2] In this present case, TOCU could show neither the carotid bifurcation nor the petrous portion of the ICA. Therefore, a whole image of EICAD, including an intimal tear, could not be revealed by this procedure.

In conclusion, TOCU might represent a useful procedure for not only early diagnosis, allowing potential preventive treatments to be initiated as soon as possible, but also follow-up of EICAD.

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Multiple Acute Ischemic Brain Lesions and Increased Fluorodeoxyglucose Uptake in the Ascending Aorta

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A 65-year-old hypertensive man was hospitalized with sudden disturbance of consciousness and left hemiparesis. Diffusion-weighted imaging demonstrated multiple small areas of acute infarction in the left cerebellar hemisphere and in the distributions of the middle cerebral arteries. These findings were highly suggestive of an embolic mechanism. To rule out nonbacterial thrombotic endocarditis, we performed transesophageal echocardiography (TEE), and [^{18}F]fluorodeoxyglucose positron emission tomography (FDG PET) was performed for the detection of occult cancer [1]. TEE was normal, but FDG PET demonstrated an increased FDG uptake in the thoracic aorta (fig. 1a). Dissection in the ascending aorta was suspected and confirmed by thoracic computed tomography. Total arch replacement was performed, and histopathological examination demonstrated hematoma formation, macrophages in the media (fig. 1b), and foam cells in the intima with increased FDG uptake in the dissecting aorta, each of which could be at least partially responsible for the increased FDG uptake [2].

The sensitivity of TEE for the evaluation of lesions in the ascending aorta can be limited by artifacts [3]. Although FDG PET is not used as part of the routine evaluation of stroke patients, this case points out the possible significance of an increased FDG uptake in the aorta of patients with probable embolic stroke.

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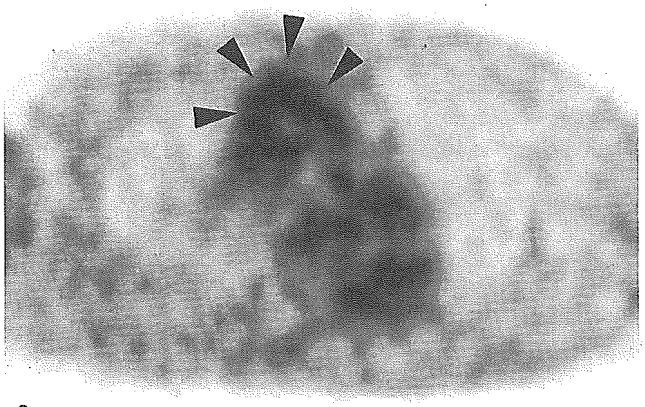

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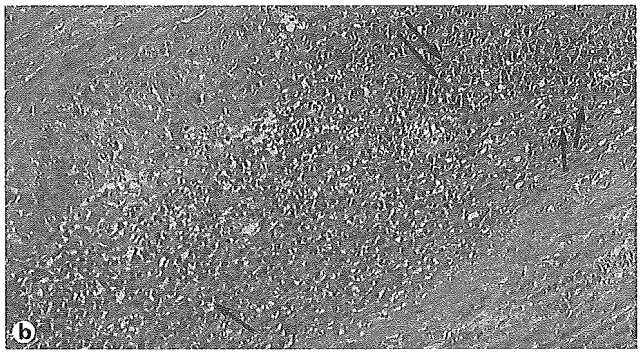

Fig. 1. a Axial FDG PET showing diffuse FDG uptake in the thoracic aortic wall (arrowheads). **b** Arrows indicate representatives of macrophages englobing hemosiderin in the hematoma of the tunica media. HE. ×200.

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Brain Embolism Caused by a Mobile Aortic Thrombus with Iron Deficiency Anemia

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Atherosclerotic lesions at the aortic arch are recognized as potential sources of embolic stroke [1]. There were some reports of embolic stroke caused by a mobile thrombus located at the aortic arch (MTAA) [2–5]. Although almost all these patients had marked atherosclerotic changes, a few reports demonstrated that an MTAA was not accompanied by atherosclerotic changes and had no definite etiology [4, 5]. Furthermore, previous studies suggested an association between thrombogenesis and anemia [6, 7]. We report 2 female patients with iron deficiency anemia (IDA) who developed brain embolisms caused by an MTAA without having atherosclerotic changes in the aortic arch.

Report of 2 Cases

Patient 1. A 50-year-old housewife was admitted to our hospital because she abruptly developed a disturbance of consciousness. She had suffered from anorexia since the age of 17 years and from occasional hematochezia for 2 months before the admission. The patient had no established risk factors associated with cardiovascular diseases except for smoking. Her family history was not particular. On physical examination, she was emaciated (body mass index 15.2) and pale. Her pulse was regular (80/min), and the blood pressure was 120/70 mm Hg. There were systolic cardiac murmurs and no carotid bruits. Neurological examinations revealed that she was drowsy and had aphasia and a right-sided hemiplegia. Laboratory examinations (table 1) demonstrated severe IDA, mild thrombocytosis, a hypercoagulable state and a low plasma level of protein S activity (PSA). Her parents' PSAs were normal.

On the day of admission (day 1), brain diffusion-weighted imaging showed an acute infarction in the left middle cerebral artery area (fig. 1a). On magnetic resonance angiography (MRA), the left internal carotid artery was occluded. There was no evidence of atheromatous changes in intracranial or extracranial arteries on carotid ultrasonography or MRA. Transesophageal echocardiography (TEE) demonstrated a mobile mass (18 mm × 8 mm) in the aortic arch (fig. 1b). Although the attachment of the mobile mass could not be evaluated by TEE, no other abnormalities, such as atherosclerotic changes, could be detected on TEE. Thoracic cine-magnetic resonance imaging (CMRI) revealed a club-shaped floating mass (fig. 1c), which was attached to the wall of the ascending aorta, but there were no abnormalities on the internal surface of the aorta, including the attachment of the mass. Extensive examinations were made to search for a cause of the IDA, but no abnormality was detected except for internal hemorrhoids. Her IDA improved with blood transfusion, and heparin administration was started. On day 19, the mass was no longer detected on TEE and CMRI. The plasma levels of thrombin-antithrombin III complex and D-dimer normalized.

The patient's hospital course was uneventful. She became used to walk with a cane. She was discharged from hospital on warfarin therapy. One year after the stroke, warfarin sodium was switched to aspirin. Reexamination of her PSA showed it improved to the normal range (76%). During 2 years of follow-up, the patient had no recurrence of stroke, thrombophilia or IDA.

Patient 2. A 41-year-old housewife was admitted because of sudden onset of dysarthria and right-sided hemiplegia. Her medical history included epimenorrhagia since the age of 20 years. The patient had no established risk factors associated with cardiovascular diseases except for smoking. Her uncle had an ischemic stroke. On physical examination, her body mass index was 24, the pulse was regular (64/min), and the blood pressure was 128/64 mm Hg. Her palpebral conjunctiva was pale, suggesting anemia. She had mild

Table 1. Laboratory data of the two patients

	Normal range	Patient 1	Patient 2
RBC count × 10,000/μl	380–510	333	401
Hemoglobin, g/dl	12.0–16.5	5.5	7.9
Hematocrit, %	35–45	20	25
MCV, μm^3	85–100	62	61
MCH, pg	27–33	16.7	18.9
Platelet count × 10,000/μl	15.0–35.0	42.0	36.0
Reticulocytes, ‰	5–20	10	23
Fe, μg/dl	43–172	16	9
Ferritin, μg/ml	0–429	21	2
TAT, μg/ml	<2.00	6.08	3.62
D-dimer, μg/ml	<1.0	5.2	1.2
Protein S activity, %	65–105	36	54
CRP, mg/dl	<0.6	0.09	0.05

RBC = Red blood cells; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; TAT = thrombin-antithrombin complex; CRP = C-reactive protein.

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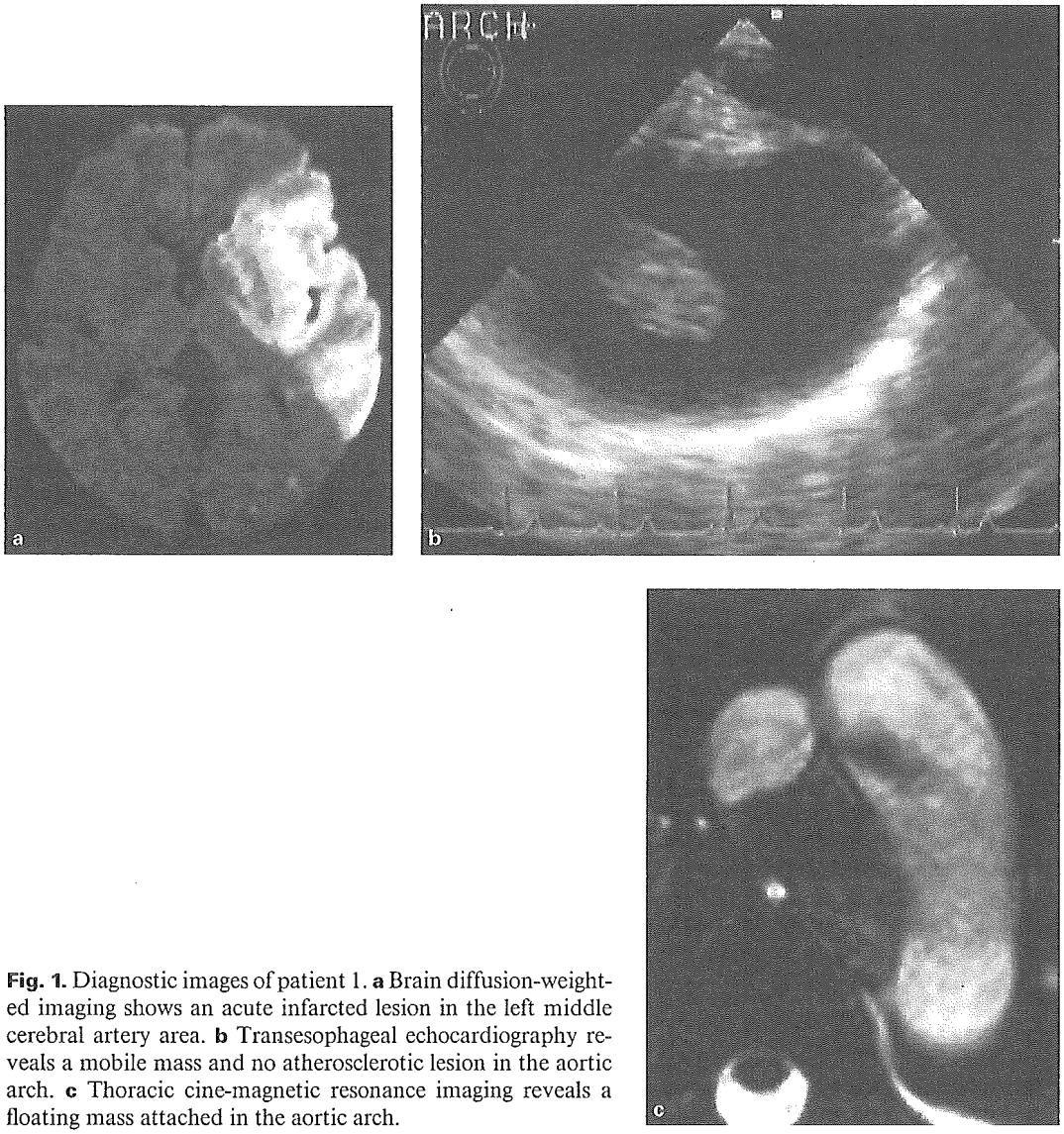

Fig. 1. Diagnostic images of patient 1. **a** Brain diffusion-weighted imaging shows an acute infarcted lesion in the left middle cerebral artery area. **b** Transesophageal echocardiography reveals a mobile mass and no atherosclerotic lesion in the aortic arch. **c** Thoracic cine-magnetic resonance imaging reveals a floating mass attached in the aortic arch.

systolic cardiac murmurs and no carotid bruits. Neurological examinations revealed dysarthria and a right-sided hemiplegia. Laboratory examinations (table 1) demonstrated IDA, mild thrombocytosis, a hypercoagulable state and a low plasma PSA level. Her parents' PSAs were not measured.

On the day of admission (day 1), brain diffusion-weighted imaging showed acute infarctions in the bilateral cerebellum and the territories of the left middle cerebral artery and the left anterior cerebral artery (fig. 2a). MRA demonstrated a left anterior cerebral artery occlusion. There was no evidence of atheromatous changes in intracranial or extracranial arteries on carotid ultrasonography or MRA. TEE revealed a mobile mass (5 mm × 10 mm) in the aortic arch (fig. 2b). No other abnormalities, such as atherosclerosis, were revealed in the aortic arch, including the attachment of the mass. Heparin administration was started, and the mobile mass could not be detected by thoracic CMRI or TEE on day 7. Thoracic CMRI also showed no abnormalities on the internal surface of the aorta. The plasma levels of thrombin-antithrombin III complex and D-dimer normalized. Further examinations were done to search for a cause of the IDA, and the patient was found to have adenomyosis uteri.

A month later, the patient's IDA was successfully treated with ferrotherapy. With a mild right-sided hemiplegia she was discharged from hospital taking warfarin and ferrotherapy. Six months after stroke onset, the patient had no recurrence of stroke or IDA. Then, reexamination after switching warfarin sodium to aspirin showed that PSA had normalized (80%).

Discussion

In the present cases, there were no causes of stroke, such as atheromatous diseases, other than a mobile mass attached to the aortic arch. So, we considered that embolic occlusion caused by fragments

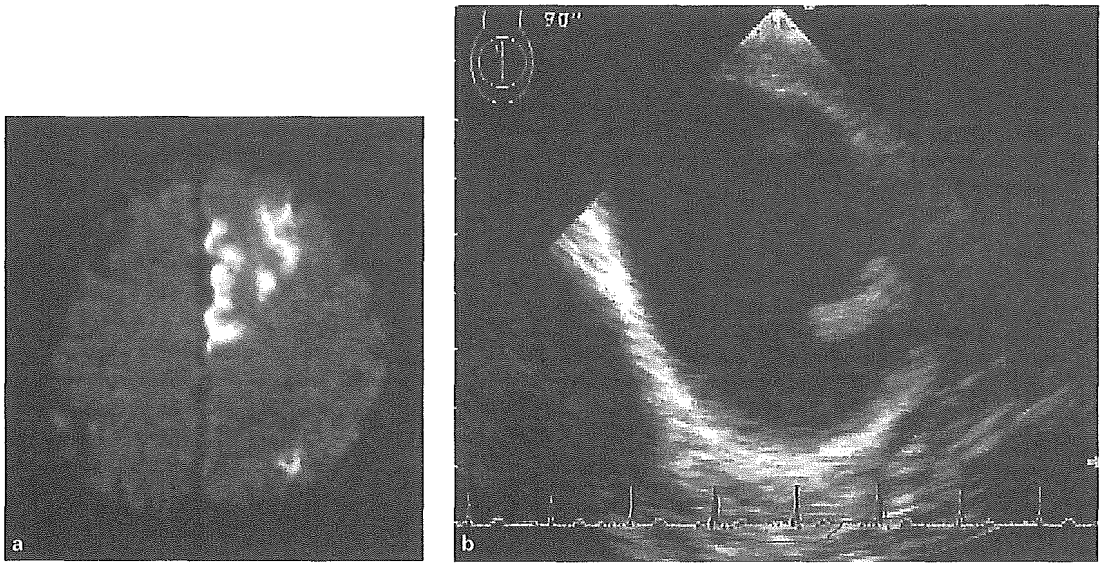

Fig. 2. Diagnostic images of patient 2. **a** Brain diffusion-weighted imaging shows acute infarcted lesions in the territories of the left middle cerebral artery and the left anterior cerebral artery. **b** TEE reveals a mobile mass and no atherosclerotic lesion in the aortic arch.

of the mass would be the most likely mechanism of their neurological events. Although it was initially difficult to determine whether the mass was a thrombus or a tumor, the diagnosis of a thrombus was made because the mass disappeared with anticoagulation therapy.

There were some common denominators in these cases, including middle age, female gender, no cardiovascular risk factors except for smoking, the complication of severe IDA and a hypercoagulable state at stroke onset, and an MTAA without atherosclerotic changes as a potential embolic source.

In previous studies, embolic stroke associated with an MTAA usually showed atherosclerotic changes at the origin of the MTAA [2–5]. Therefore, it seems that atherosclerosis plays a major role in the formation of a mobile thrombus at the aortic arch. However, in those studies, an MTAA was detected in a small number of cases without identifiable atherosclerotic changes in the aorta [4, 5]. There are scattered reports of various conditions other than atherosclerotic changes that may predispose to intra-aortic thrombosis, such as thrombocythemia [8], polycythemia [9], antithrombin III deficiency [10], protein C deficiency [4], antiphospholipid antibody syndrome [4], malignant tumor [2], blunt chest trauma [11], chest gunshot wound [12] or systemic fungal infection [13]. (However, these abnormalities were not seen in the present cases.) Thus, factors other than severe atherosclerosis may play an alternative role in the MTAA formation.

In the common denominators in the present cases, we considered that severe anemia was noteworthy for the MTAA formation. There are several mechanisms that may explain the association of thrombus formation in the aortic arch with anemia. Firstly, anemia following acute bleeding increases platelet adhesiveness [6] and decreases fibrinolytic activity [7]. The concomitant presence of reactive thrombocytosis may have a role in inducing intravascular thrombogenesis [14]. Secondly, anemia may induce a hyperkinetic circulatory state. In the present cases, patients had cardiac systolic murmurs. Arterial bruits are common in patients with severe anemia [15] and are a physical sign of turbulent flow due to increased hemodynamic force. An increased hemodynamic force has been shown to upregulate the endothelial adhesion molecule genes [16, 17], which may induce local immunologic-inflammatory reactions leading to thrombogenesis.

It was unclear why the thrombus appeared in no other parts but the aortic arch in our patients. Laperche et al. [4] reported that 23 patients without marked atherosclerotic changes had MTAA detected among 27,855 TEE examinations and that they did not have any other visible sites of thrombi on TEE. So, the aortic arch may be a part where the thrombus appears more frequently than in other parts of the aorta.

Both presented patients had low PSA levels on admission without any concomitant conditions, such as hepatopathy, taking oral contraceptives or warfarin, pregnancy, systemic lupus erythematosus or nephropathy. In patient 1, the low PSA level was found not to be hereditary. In addition, both PSA levels in the present cases normalized after anticoagulant therapy. Thus, the low PSA levels seen after stroke onset might reflect PSA consumption due to a hypercoagulable state.

Endothelial cell adhesion, which plays one of the important roles in thrombogenesis, could be caused by inflammation. Recently, it has been reported that human aortic endothelial cell adhesion was induced by C-reactive protein which is a novel marker of inflammation [18]. However, C-reactive protein elevations were not demonstrated in the current 2 cases (table 1).

In conclusion, we demonstrated 2 stroke patients in whom an MTAA was considered as the most likely source of emboli. These MTAAs had no relation to the atherosclerotic aorta but to severe

IDA. Severe IDA might be one of the factors implicated in the formation of MTAA. Therefore, if the cryptogenic stroke patient has severe IDA, the aortic arch should be explored for a mobile thrombus.

Acknowledgement

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Hemopericardium following Intravenous Thrombolysis for Acute Ischemic Stroke

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An 83-year-old woman with a history of hypertension and hyperlipidemia presented with acute left hemiparesis, hemisensory deficit and hemineglect within three hours of symptom onset. On arrival to the emergency room, she was noted to be moderately bradycardic and hypotensive. Her hypotension and bradycardia were attributed to her possible randomization to the active treatment arm of a prehospital neuroprotective trial involving magnesium, in which she had been enrolled [1]. Mild-to-moderate hypotension and bradycardia are known side effects of magnesium treatment. Both blood pressure and heart rate normalized after she received intravenous fluids. Admission cardiac examination, EKG and cardiac enzymes were normal. Head CT revealed neither hemorrhage nor early ischemic changes. The patient met all qualifying criteria for intravenous tissue plasminogen activator (IV t-PA). Although she was of advanced age, her severe stroke and good premorbid functioning as well as studies suggesting that the risks and benefits of intravenous t-PA in ischemic stroke patients aged ≥80 years, are comparable to those in younger individuals when administered according to established protocols [2–4], she was given IV t-PA according to the NINDS protocol [5].

Initially, the patient had a good response to the t-PA with mild improvement in function of her left hand and speech. However, 1 h and 15 min after the start of administration of t-PA, the patient became extremely hypotensive. Aggressive fluids were administered along with calcium gluconate in order to reverse any untoward effects of possible magnesium treatment. However, her hypotension persisted. A repeat EKG showed no signs of acute cardiac ischemia. Dopamine and norepinephrine infusions were then started, without significant improvement of her blood pressure. Emergent bedside transthoracic echocardiogram (TTE) was performed which showed a posterior pericardial effusion with fibrin clots and evidence of right atrial and ventricular collapse. A second set of cardiac enzymes ordered 3 h after the first set were normal. The patient proceeded to enter into pulseless electrical activity and then asystole, despite aggressive cardiopulmonary resuscitation. The patient's family declined autopsy.

Discussion

The risk of symptomatic intracerebral hemorrhage and systemic bleeding requiring transfusion, surgery or other aggressive management following administration of IV t-PA in ischemic stroke has been well described [5]. However, cases of hemopericardium and cardiac tamponade after intravenous thrombolysis for ischemic stroke are extremely rare [6]. These complications have been more broadly reported in the cardiac literature, in patients who received thrombolysis after acute myocardial infarction [7], and in patients with known pericarditis [8]. However, since the institution of IV t-PA as a standard treatment for acute ischemic stroke in 1996, there has only been one report describing 3 such cases [1]. This

4. EBM and Current State in Japan of Thrombolytic Therapy for Acute Ischemic Stroke

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Key words: acute ischemic stroke, penumbra, intracranial hemorrhage, tissue plasminogen activator

Introduction

The new era has began for acute stroke management since intravenous thrombolytic therapy using tissue plasminogen activator (t-PA) was reported to be effective in increasing a complete or near-complete recovery in 3 months, if administered within the initial 3 hours after stroke onset (1). The treatment is now approved for use in ischemic stroke patients in USA, Canada, and European countries. Stroke becomes a medical emergency and is called "Brain Attack". Most guidelines of stroke therapy in these countries strongly recommend the use of t-PA for patients with acute ischemic stroke (2, 3).

Favorable outcome induced by hyperacute t-PA therapy were first suggested by randomized controlled trials (RCT) carried out in Japan (4, 5). The first Japanese guideline of stroke management published in 2004 recommends the use of intravenous t-PA therapy (Grade A) and local prourokinase (proUK) therapy (Grade B) (6), although both therapies have not yet been approved in Japan.

Theory and history

The strategy of thrombolytic therapy is based on the concept that early reperfusion rescues reversibly damaged brain tissues in the ischemic penumbra (7, 8). Therefore, it is a reasonable speculation that thrombolytic therapy can promote early reperfusion, resulting in good clinical outcome.

Clinical trials with the first generation thrombolytic agents, streptokinase (SK) and urokinase (UK) failed to show favorable results but caused increases in symptomatic intracranial hemorrhage and in the death rate. In the 1980's, it was demonstrated with RCTs that the 2nd generation thrombolytic agents such as alteplase could improve outcome in patients with acute coronary thrombosis. The agents, then, began to be tested in acute ischemic stroke patients.

The results of several phase 3 RCTs with intravenous t-PA for the urgent treatment of patients with stroke have been reported (1, 5, 9, 10). Among them, only the NINDS trials could demonstrate a significant increase in patients with very favorable outcome at 3-months (1). Cost-effectiveness and long-lasting efficacy were also demonstrated in subanalysis of the study (11, 12). Other trials with a 6-hour time window, however, could not demonstrate the effectiveness and safety of t-PA therapy (9, 10).

The Prolysis in Acute Cerebral Thromboembolism II (PROACT II) trial was the first RCT in which intraarterial thrombolysis was shown to have a benefit in patients who have had a stroke caused by occlusion of the middle cerebral artery (MCA) and were treated within 6 hours after clinical onset (13). However, the therapy has not been approved in the United States.

In Table 1, the results of major RCTs with thrombolytic therapy for acute ischemic stroke patients reported in the English language literature are summarized.

Guidelines

In most guidelines of acute stroke management in the North America and Europe, intravenous t-PA (0.9 mg/kg, maximum dose 90 mg) is strongly recommended for carefully selected patients who can be treated within 3 hours of onset of ischemic stroke (Grade A) (2, 3). The decision for treatment with t-PA should be based on several clinical features, mostly based on the protocol of the NINDS study. A recent case series indicated that implementation of intravenous t-PA therapy may not always be easy and safe, but in other series the safety and efficacy of this treatment were similar to those in the NINDS trial (14, 15). Violation of the NINDS protocol, particularly in the case of delayed treatment after 3 hours of stroke onset, may cause an increase in patients with symptomatic intracranial hemorrhage and result in a poor outcome (16).

As mentioned earlier, the first Japanese guideline of stroke management published in 2004 strongly recommends the use of intravenous t-PA therapy (Grade A) and local prourokinase (proUK) therapy (6). The recommendation, however, duplicates the statement of the American guideline. No studies demonstrating high-level evidence, nor guidelines specific to Japanese patients have been available.

Current status of thrombolytic therapy in Japan

There were no studies to clarify the state of stroke management in Japan. To respond to this question, the Japan

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Table 1. Summary of Major Randomized Clinical Trials with Thrombolytic Therapy

Trials	No. of patients	Time of therapy	Dose	Results	Intracranial hemorrhage
1. t-PA intravenous therapy*					
JTSG (Japan)	98	<6 hs	20 MU	Effective?	unchanged
NINDS (USA)	624	<3 hs	0.9 mg/kg	Effective	increase
ECASS-I (Europe)	620	<6 hs	1.1 mg/kg	Not effective**	increase
ECASS-II (Europe)	800	<6 hs	0.9 mg/kg	Not effective***	increase
ATLANTIS (USA)	579	3～5 hs	0.9 mg/kg	Not effective	?
2. SK intravenous therapy					
ASK (Australia)	340	<4 hs	1.5 MU	Harmful	increase
MAST-I (Italy)	622	<6 hs	1.5 MU	Harmful	increase
MAST-E (Europe)	270	<6 hs	1.5 MU	Harmful	increase
3. proUK intraarterial (local)					
PROACT-II (USA)	180	<6 hs	9 mg	Effective	increase

*JTSG (Japan Thrombolysis Study Group) used duteplase, and other trials used alteplase. **Effective if exclude 109 cases with protocol violation. ***Partly effective in some outcome measures.

Multicenter Stroke Investigators Collaboration, so-called J-MUSIC, conducted a multicenter study on stroke management from May 1999 to April 2000 (Chief Investigator: Yamaguchi T) (17). In 156 hospitals all around Japan, 16,922 acute ischemic patients admitted within the initial 7 days were consecutively registered. In the data of J-MUSIC, t-PA was administered intravenously to only 0.3%. In contrast, intraarterial t-PA (0.5%) or UK (1.6%) therapy was given to 2.5% of the patients.

In the database of J-MUSIC, we had 91 patients with acute ischemic stroke who were 20 to 75 years of age, admitted within the initial 4.5 hours, had a NIHSS score greater than 4 but less than 23 on admission, and treated with intraarterial UK therapy. We also selected from the J-MUSIC database 182 control patients who had similar clinical backgrounds but were not treated with thrombolytic agents, then compared the clinical outcome between the cases and controls. Patients who had a good outcome at discharge were significantly more frequent in the patients treated with intraarterial UK than in the controls (data submitted to an English journal).

Clinical studies in Japan

The suggestion by the case-control study of the J-MUSIC is now tested with a RCT, so-called MELT-Japan (MCA-Embolism Local Fibrinolytic Intervention Trial Japan), chaired by Professor Ogawa. The detailed information of the study is opened to the public in the MELT-Japan homepage [http://melt.umin.ac.jp (Feb 8, 2005)]. The study is designed to consist of a total of 200 patients and is now on going.

A phase III trial using open-labeled, single-dose alteplase has just been finished in Japan (Japan Alteplase Clinical Trial, J-ACT). The study was designed to confirm the results of the t-PA group in the NINDS study. The study protocol was almost compatible to that of the NINDS study, except for several modifications. They included lower dose administration of alteplase (0.6 mg/kg) in the J-ACT than that (0.9 mg/kg) in the NINDS study. The results of the J-ACT were briefly presented in the joint symposium of the 29th annual meeting of the Japan Stroke Society and the 33rd annual meeting of the Japanese Society of Cerebral Stroke (Nagoya, March 19, 2004). The clinical background of the patients was similar to those in the NINDS study. Frequencies of very favorable outcome at 3-months and symptomatic intracranial hemorrhage were comparable between the studies. Mortality at 3-months, however, was less frequent in the J-ACT.

The J-ACT results mentioned above are very promising. The MELT-Japan will hopefully provide the class I evidence for local UK therapy within 6 hours after stroke onset in the near future. A great amount of investigative work will be needed to validate the potential of thrombolytic therapy for acute stroke patients in Japan. We are now entering an exciting new era for stroke management.

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5. Future Aspects of Gene Therapy in Acute Ischemic Stroke

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Key words: gene therapy, brain ischemia, macrophage, neurogenesis

Neural stem/progenitor cells remain in the adult mammalian brain, including the human brain. Neurogenesis continues throughout life in the two restricted zones, the hippocampal subgranular zone (SGZ) and the rostral migratory stream, where newly generated immature neurons migrate from the anterior subventricular zone (SVZ) into the olfactory bulb. Brain injury including ischemia stimulates neurogenesis in the SGZ and SVZ (1, 2). Therefore, therapeutic strategy for enhancing neurogenesis after ischemia may be of value for promoting functional recovery in stroke patients with neurological deficits. Intracerebral or intraventricular injections of neurotrophic factors could stimulate neurogenesis in the ischemic hippocampus and caudoputamen (3, 4). However, dependence on invasive surgical procedures for delivery could limit clinical application (Fig. 1A, B). Therefore, non-invasive, safe, and inexpensive strategies would be required for clinical application for enhancing neurogenesis in stroke patients. Several previous studies including our own have demonstrated that circulating monocytes or macrophages begin to infiltrate ischemic tissue after infarction develops (5). Peripheral blood mononuclear cells and macrophages have drawn much attention as novel cellular vehicles for gene therapies in which these cells are genetically modified *ex vivo* and then reintroduced into the body (6). Furthermore, cationic liposome/DNA complexes have been shown to be capable of transfecting monocytes/macrophages *in vivo* in blood, liver, and spleen (7). These observations suggest that after systemic intravenous injection of a cationic liposome/DNA complex, circulating monocytes/macrophages could take up the introduced gene and infiltrate infarcted tissue. Therefore we tried to develop the systemic gene therapy using infiltrating macrophages as cell vehicles. We used an enhanced green fluorescent protein (EGFP) expression vector complexed with cationic liposomes for systemic gene therapy. After systemic administration of pIRES-EGFP plasmid vector with Lipofectin into normal rats, no EGFP-positive cells or macrophages were observed in intact brain. However, macrophages markedly accumulated in the brain tissue once infarct developed (Fig. 1C), and large numbers of EGFP-positive cells were detected in the marginal zone of the infarct. Expression of the exogenous EGFP gene was

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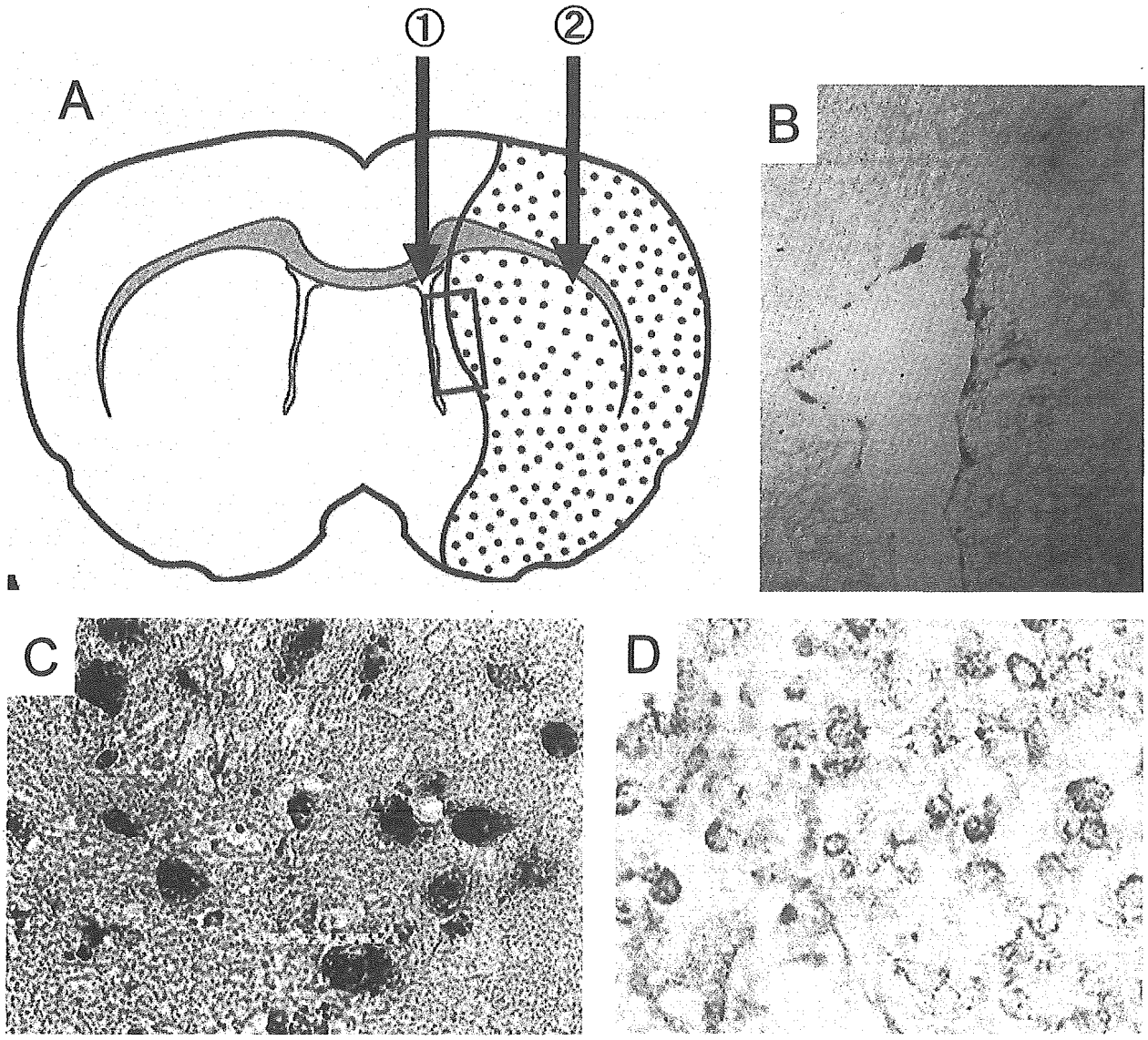

Figure 1. The diagram depicts sections of the rat brain after middle cerebral artery (MCA) occlusion with the infarct shown as stippled (A). The border area is indicated by the rectangular box in the striatum. Intraventricular (1) or intracerebral (2) injection is widely used for gene transfer into the brain. Intraventricular administration of adenoviral reporter gene resulted in expression of exogenous gene on the wall of the lateral ventricule (B). Macrophages accumulating along the margin of the evolving infarct are shown with anti-Mac2 antibody in (C). Immunohistochemistry with anti-EGFP antibody was used to confirm EGFP protein expression in the ischemic caudoputamen after intravenous injection of pIRES-EGFP plasmid vector (D).

confirmed immunohistochemically using an anti-EGFP antibody (Fig. 1D). Most EGFP-positive cells expressed monocyte/macrophage specific antigens. To deliver exogenous FGF-2 gene to the infarct, we injected pIRES-FGF2-EGFP plasmid. Marked expression of both FGF-2 and EGFP was observed in the infarct (Fig. 2A–C). Administration of pIRES-FGF2-EGFP plasmid increased the number of neural progenitor cells (Fig. 2D, 2E) in the lateral wall of the SVZ after MCA occlusion (Fig. 2F).

Gene therapy for stroke holds promise because of its ability to induce expression of desired molecules by cells for a long period. Gene transfer for neurotrophic factors (8), anti-apoptotic protein (9), and heat shock protein (10) can ameliorate ischemic brain damage when administered before or even after induction of ischemia. Post ischemic treatment could be given to stroke patients provided that efficacy and safety were proven. However, the viral vectors such as herpes simplex virus and adenovirus used in experimental stud-

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3D Rotational Angiographic Demonstration of Dissection of the Anterior Cerebral Artery

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Introduction

Dissection of intracranial arteries presents with a much less specific angiographic appearance than that of the extracranial portion of the cervicocephalic artery, rendering a correct diagnosis using common diagnostic tools difficult. We describe the usefulness of three-dimensional rotational angiography (3D-RA) for visualizing the double lumen sign, which is the pathognomonic finding of arterial dissection.

Case Report

A 59-year-old man developed sudden onset of weakness in the left lower limb and neck pain after karaoke singing. He was admit-

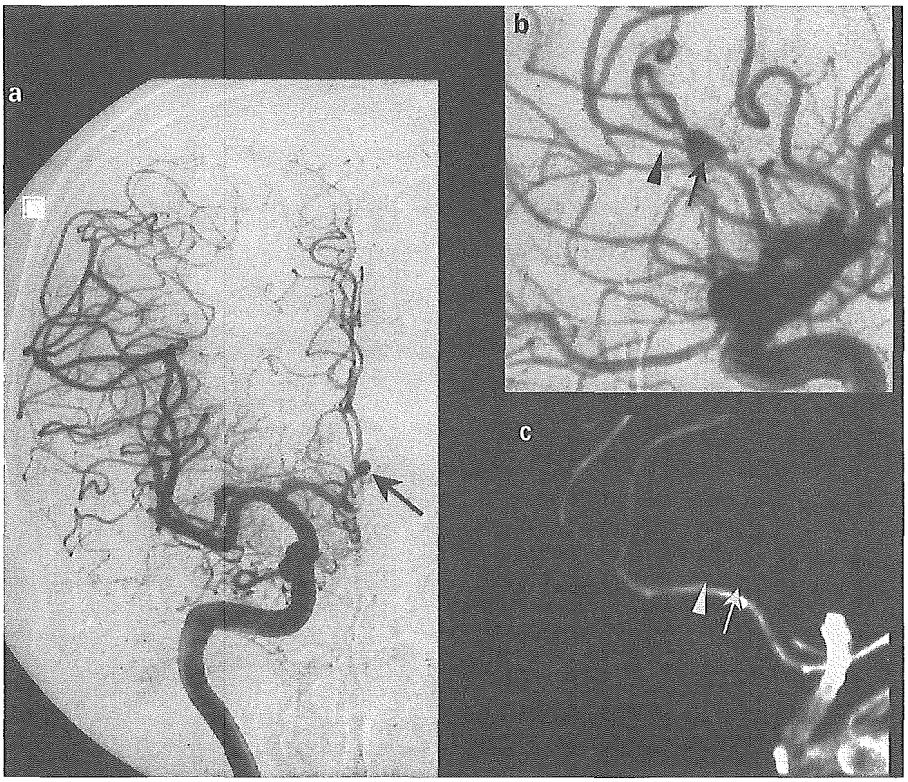

Fig. 1. Conventional cerebral angiography and MRA. Right carotid conventional angiography 30 days post-ictus, anteroposterior view (**a**) and lateral view (**b**), revealing aneurysmal dilatation of the right proximal A2 portion (arrow), followed by segmental arterial stenosis (arrowhead). MRA (**c**) shows aneurysmal dilatation of the right proximal A2 portion (arrow) with segmental arterial stenosis (arrowhead).

ted to our stroke care unit the following day. Blood pressure was 160/90 mm Hg. General physical examination revealed no abnormalities.

Upon neurological examination, the patient was alert and fully oriented. He spoke clearly and fluently. Cranial nerve functions were normal. Muscle strength testing revealed left-sided hemiparesis with crural predominance. Coordination and sensation to light touch and pinprick were normal. Deep tendon reflexes were exaggerated on the left side. Plantar responses were extensor on the left. No signs of callosal disconnection syndrome were observed.

Magnetic resonance (MR) images of the brain, performed 2 days post-ictus, demonstrated fresh brain infarction in regions supplied by the right ACA. Conventional cerebral angiography, performed 2 days after onset, revealed slightly dilatation of the right proximal A2 portion, followed by segmental narrowing. We suspected the residual stenosis by brain embolism or dissection of the ACA. To confirm the findings, angiography was performed 30 days after onset which revealed aneurysmal dilatation of the right proximal A2 portion, followed by segmental narrowing (fig. 1a, b). Both MRI and magnetic resonance angiography (MRA) (fig. 1c) failed to detect the double lumen sign. Examination using 3D-RA with a standard Integris BV5000 biplane system (Philips Medical System, Best, The Netherlands) demonstrated the same abnormalities mentioned above (fig. 2a, b), and clearly identified an intimal flap (fig. 2c), leading to a diagnosis of dissecting aneurysm.

Discussion

Cerebral arterial dissections are being detected with increasing frequency, which is partially attributable to increasing interest in the clinical and radiological features of this disorder, and also to the increasing availability of non-invasive neuroimaging techniques, which are steadily improving in quality. However, dissection involving small-caliber vessels, such as the intracranial arteries, displays a non-specific angiographic appearance, and the diagnostic roles of MRI and MRA remain limited in such cases. Many patients with dissection involving these vessels might have been overlooked [1]. Chaves et al. [2] recently reported on 10 patients with spontaneous dissection of the intracranial portion of the internal carotid artery (ICA). They emphasized that ICA dissection should be considered as a differential diagnosis for intracranial ICA stenosis or occlusion.

The 'string sign' [3], 'rosette sign' [4] and 'pearl reaction' [5] have been reported as angiographic characteristics of arterial dissections. However, these findings are not considered particularly specific, as they are also seen in atherosclerotic vascular diseases [6]. Although the double lumen sign, which is visible flow in both the true and false lumen [6], has been suggested to be a pathognomonic, it is rarely seen in intracranial arteries [1]. To the best of our knowledge, only 4 cases of the double lumen sign in the ACA have been reported in the English literature [7–9]. Kazui et al. [10] reported 17 patients with solitary infarction in the territory of the ACA, including 4 of undetermined etiology. One patient had an A2

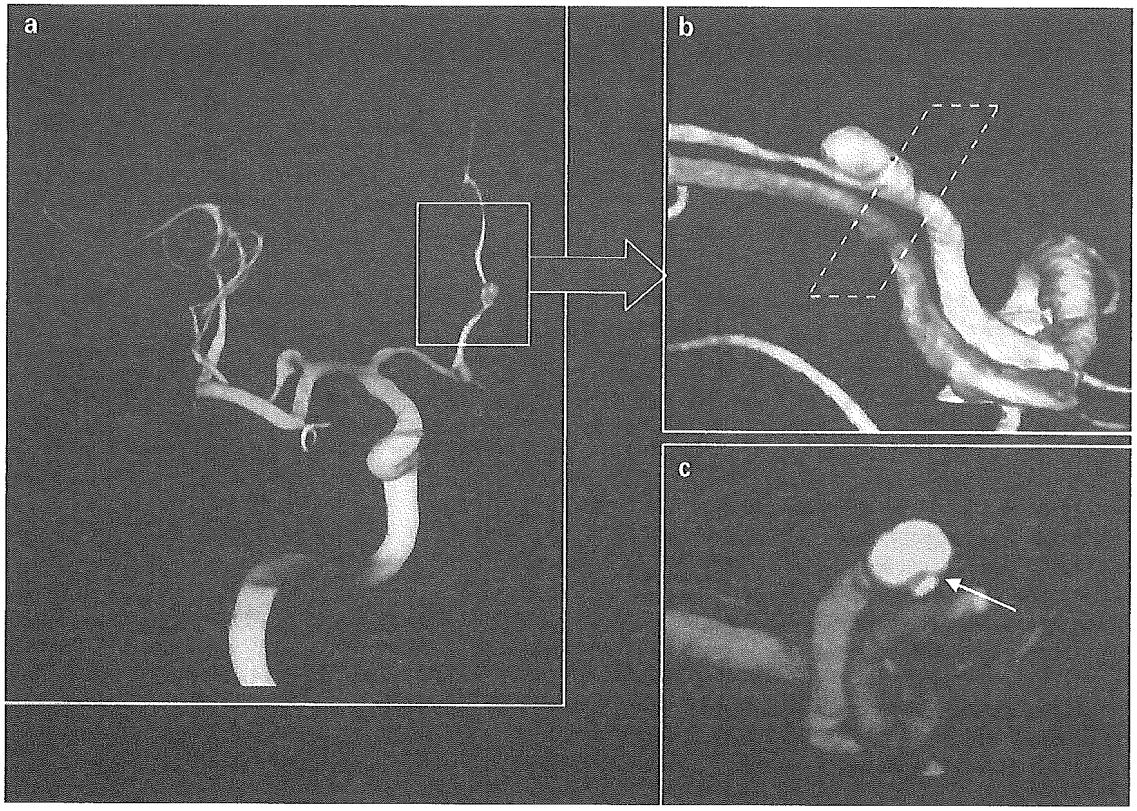

Fig. 2. Three-dimensional rotational angiography. Right carotid 3D-RA displaying aneurysmal dilatation of the right proximal A2 portion followed by segmental arterial stenosis (**a**, **b**). Cut plane (**c**) demonstrating intimal flap (arrow).

segment which was initially occluded and subsequently reopened. The other 3 had A2 segments which were initially dilated and then later restored to a normal state. As vascular changes in these cases were restricted to the ACA, and resolution of stenosis or occlusion has been considered a reliable angiographic sign of arterial dissection, they concluded that diagnoses of isolated ACA dissection seemed reasonable [11]. Our case presented a definite diagnosis, because the double lumen sign was demonstrated using 3D-RA. This sign was not observed using conventional angiography, MRI or MRA.

Rotational angiography was proposed by Cornilis et al. [12] in 1972, and clinical use was reported by Thron and Voigt [13] in 1983. Several reports have confirmed the superiority of this technique to conventional digital subtraction angiography for assessment of the aneurysmal neck and fundus [14, 15].

Arterial dissections can cause three types of stroke: in situ infarct; distal embolization by thrombus originating from the site of dissection, and subarachnoid hemorrhage caused by rupture of the dissecting aneurysm. As all three variations are prone to occur soon after dissection, rapid and correct diagnosis is quite important in the acute phase of stroke. The risks of angiographic complications will be considered constantly and the benefit of 3D-RA should be balanced with the risks.

We have described herein the usefulness of 3D-RA for visualizing pathognomonic findings of arterial dissection, which accomplishes the correct diagnosis where other neuroimaging techniques fail.

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C2 Segmental Type of Vertebral Artery with Recurrent Embolic Strokes

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Introduction

'C2 segmental type of vertebral artery' is a remnant metameric artery that courses through the intervertebral foramen between the atlas and axis, where it penetrates the dura mater. The atlantoaxial joint, where most of the neck rotation is generated, is one of the sites most susceptible to traumatic injury of a vertebral artery (VA). C2 segmental type of VA may, thus, be vulnerable to trauma by neck rotation.

We report a patient with recurrent embolic strokes confined to the posterior circulation. The patient had bilateral C2 segmental type of VA and her left VA showed an irregular configuration at the intervertebral foramen between the atlas and axis. The possibility of brain ischemia in a setting of C2 segmental type of VA is discussed.

Case Report

On January 7, 2003, a 52-year-old woman was admitted to our hospital because of sudden diplopia, ataxia and left facial numbness. She had no history of hypertension, diabetes mellitus, hyperlipidemia, or arrhythmia, but she had been receiving chiropractic treatment for several years.

The patient had been well until 4 years before admission, when she abruptly noted diplopia, which completely disappeared in a few days. A year later, she suddenly fell over as she rotated her head rightward while closing a door. Six months later, a dizzy sensation abruptly developed, followed by dysarthria, and culminating in a complete loss of consciousness. All these symptoms subsided the following day. At every occasion, a cranial computed tomography (CT) scan was performed, each time with negative results.

Eighteen days before admission, weakness in the right arm developed, but receded a minute later. On the morning of admission, she suddenly noticed diplopia again, immediately followed by dizziness, therefore she lay down on the sofa. Two hours later, she noted numbness of the left face and clumsiness of the left hand. Three hours later, dysarthria supervened. She then consulted our hospital.

On admission, blood pressure was 124/80 mm Hg and heart rate was 60/min with regular rhythm. The chest and abdomen were normal. Cervical bruit was not audible. On neurological evaluation, the patient was alert and oriented. There were neither cognitive nor sleep disorders. Eye fields were intact. Complete upward gaze palsy was noted. Downward movement of the right eye was moderately limited, however, that of the left eye was preserved. Horizontal eye movements and convergence were intact. The pupils were equal in size and promptly reacted to light. She reported dysesthesia in the left face. There was no apparent weakness in the extremities, however, finger-to-nose test showed slight dysmetria on the left side. All tendon reflexes were normal, with negative Babinski signs.

Urine analysis, complete blood count and biochemical data were within normal ranges. Chest radiograph was normal and electrocardiogram showed normal sinus rhythm without ischemic ST changes. Cranial magnetic resonance imaging (MRI) demonstrated a high intensity area in a paramedian meso-diencephalic infarct on the right side on diffusion-weighted imaging (DWI) (fig. 1A), compatible with vertical gaze paresis. Conventional T_2-weighted images (T_2WI) depicted several old infarctions in the bilateral cerebella, right occipital cortex, and left thalamus (fig. 1B, C). In contrast, the area in the anterior circulation did not show any ischemic events.

Transesophageal echocardiography denied a responsible embolic source in either the left atrium or the aortic arch. Vertebral echogram showed normal flow velocities and peak indices in a neutral position; however, diastolic flow suddenly dropped when the neck was rotated laterally with an angle more than 60°, suggesting a possible distal occlusion (data not shown).

Then we started antithrombotic therapy intravenously and her clinical symptoms continuously improved until the seventh day. However, in spite of being under antithrombotic therapy, she suddenly complained of vertigo lasting for several hours. A second brain MRI was then performed, demonstrating new high intensity areas in the left cerebellar hemisphere on DWI (fig. 1D). MR angiography finding suggested dissecting aneurysm at left V3–V4 portion (fig. 2).

The left vertebral angiogram showed a tortuous configuration at the left V3–V4 portion (fig. 3A). When she rotated her neck right-