Table 1. Characteristics of the two groups

	UK group	Control group	p
Patients	91	182	
Gender, F/M	24/67	48/134	
Age, years (mean ± SD)	65 ± 8	65 ± 8	
NIHSS score on admission	14	14	
Interval time from stroke onset to hospital, h (mean ± SD)	1.1 ± 0.2	1.1 ± 0.3	
Interval time from stroke onset to treatment, h (mean ± SD)	3.4 ± 1.3	–	
Range	1–6		
Mega units of UK administered (mean ± SD)	0.39 ± 0.20	–	
Mean, SD, median of mRS score at discharge	2.8, 2.9, 2	3.3, 1.8, 4	0.031
mRS ≤2, %	50.5	34.1	0.012
Mortality, %	11.0	13.2	0.745
Length of hospital stay, days (mean ± SD)	46 ± 41	42 ± 42	0.347

favorable outcome were more frequently found in the UK group than in the control group (50.5 vs. 34.1%, p = 0.0124). However, no difference between the two groups was observed in the mortality rate (11.0 vs. 13.2%) or the length of hospital stay (46 ± 41 vs. 42 ± 42 days, mean ± SD).

We analyzed the relationship between time interval from stroke onset to IA-UK thrombolytic therapy and patients' outcome. The percentage of favorable outcome was higher in patients treated within 2 h of stroke onset than in those between 2–4 h and over 4 h [63% (17/27), 45% (21/47), and 47% (8/17)]. However, no significant differences among them were observed (p = 0.30).

Discussion

This case-control study based on the data from J-MUSIC demonstrates the effectiveness of IA-UK thrombolysis in acute stroke patients. Patients with IA-UK thrombolysis had an increased frequency of good outcomes, approximately 1.5 times greater than patients without IA-UK thrombolysis. However, no difference in mortality rate was observed between patients with and without IA-UK thrombolysis.

The PROACT II study [4] demonstrated a significant benefit from treatment with IA proUK in patients with a middle cerebral artery occlusion treated within 6 h of stroke onset. Their proUK group had a higher recanalization rate (66 vs. 18%) with a greater number of patients with good outcomes (mRS score 0–2) after 3 months of stroke onset (40 vs. 25%). However, the incidence of symptomatic intracranial hemorrhage was 10% in the proUK group, but only 2% in the placebo group.

In 1988, del Zoppo et al. [5] studied 20 patients and showed that local IA fibrinolytic therapy using UK or streptokinase might lead to cerebral arterial recanalization in patients with an acute carotid territory thrombotic stroke. Mori et al. [6] also assessed 22 patients and reported on the safety and efficacy of UK thrombolytic therapy for acute thromboembolic occlusion of the middle cerebral artery. Recently, Gonner et al. [8] performed IA-UK thrombolytic therapy in 43 ischemic stroke patients within 6 h of symptom onset, and reported that therapy was effective except in patients with a carotid artery occlusion. Arnold et al. [20] analyzed the clinical and radiological findings, and assessed the functional outcome 3 months after IA-UK thrombolysis for 100 consecutive patients. They concluded that IA-UK thrombolytic therapy was safe and could be efficacious. The results of the present study also lead us to conclude that local IA thrombolytic therapy using UK could be effective for acute ischemic stroke.

The therapeutic time window of IV thrombolytic therapy with rt-PA is within 3 h [1, 2]. However, in the PROACT II study proUK could be administered within 6 h of stroke onset [4]. Therefore, IA thrombolytic therapy may allow the extension of the therapeutic time window for treating acute stroke from 3 to 6 h. In the future, thrombolysis using proUK as well as UK may provide an alternative to IV thrombolysis with rt-PA in selected patients with acute ischemic stroke.

Our study has some limitations. Firstly, the aim of the J-MUSIC [15] study was to determine the present state of stroke managements in Japan, and not to investigate the effectiveness of thrombolytic therapy. Secondly, we did not require to describe the presence and frequency of symptomatic cerebral hemorrhage after thrombolytic therapy in J-MUSIC. There was a higher rate of symptomatic intracranial hemorrhage with IA proUK in PROACT II (10.2%) [4] compared to IV-rt-PA in NINDS (6.4%) [2]. However, there is no evidence that the rate of symptomatic brain hemorrhage is lower with IV thrombolysis than with IA thrombolysis. Thirdly, this was not a randomized study. Therefore, there may be some selection bias against choosing stroke patients with complications, such as heart diseases and infection. Patients with

such complications were not likely to be treated with thrombolytic therapy, and outcomes of such patients were not as good as those in patients without such complications. Furthermore, control patients did not always undergo angiography. The catheter placement itself might be benefit for destruction of the clot. Moreover, physicians who assessed patients' outcome were not blinded to treatment. Therefore, it is possible that efficacy of IA-UK thrombolysis is overestimated.

In conclusion, IA thrombolysis using UK could potentially be effective for acute ischemic stroke patients, and would allow the possible extension of the 3-h therapeutic window. This would lead to an increased number of patients being eligible for thrombolytic therapy.

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

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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, noninvasive, 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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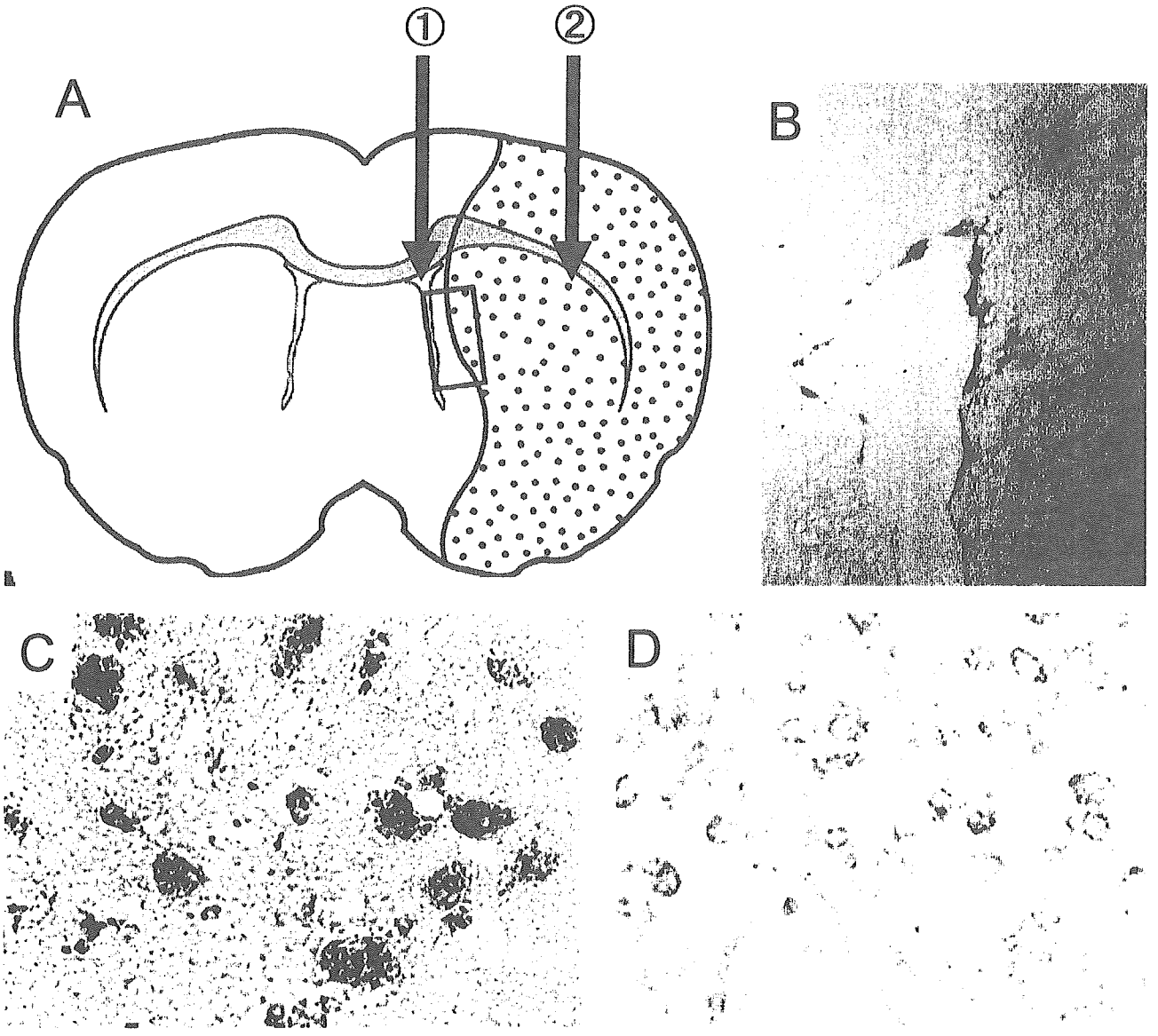

Figure 1. The diagram depicts sections of the rat brain after middle cerebral artery (MCA) occlusion with the infarct shown as stippled (A). The border area is indicated by the rectangular box in the striatum. Intraventricular (1) or intracerebral (2) injection is widely used for gene transfer into the 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), antiapoptotic 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-

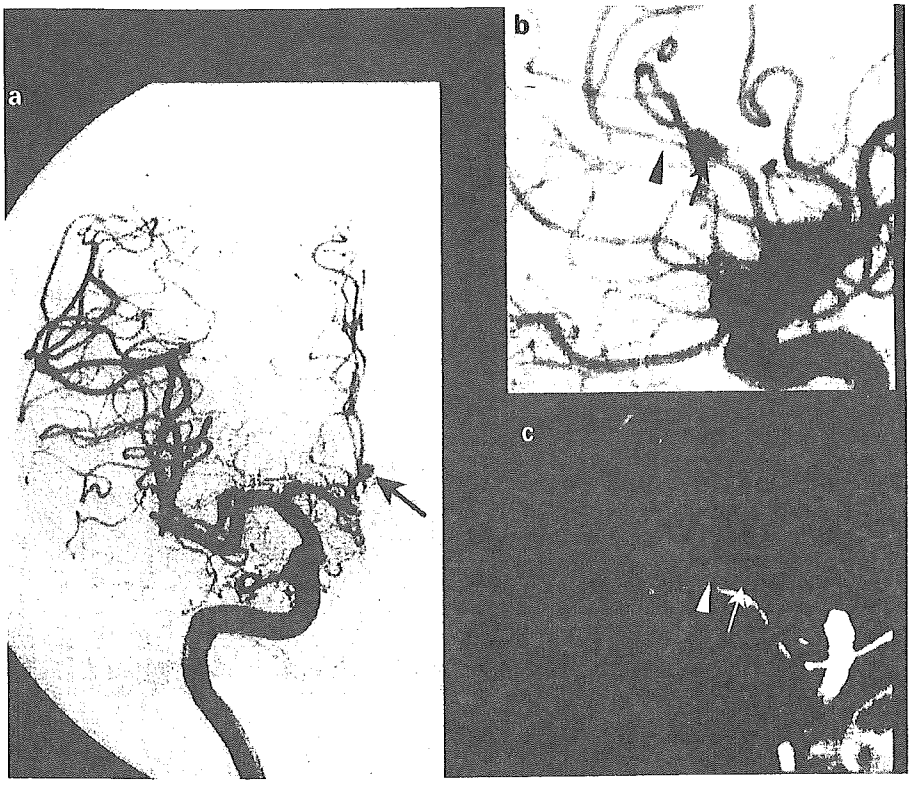

Fig. 1. Conventional cerebral angiography and MRA. Right carotid conventional angiography 30 days post-ictus, anteroposterior view (**a**) and lateral view (**b**), revealing aneurysmal dilatation of the right proximal A2 portion (arrow), followed by segmental arterial stenosis (arrowhead). MRA (**c**)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

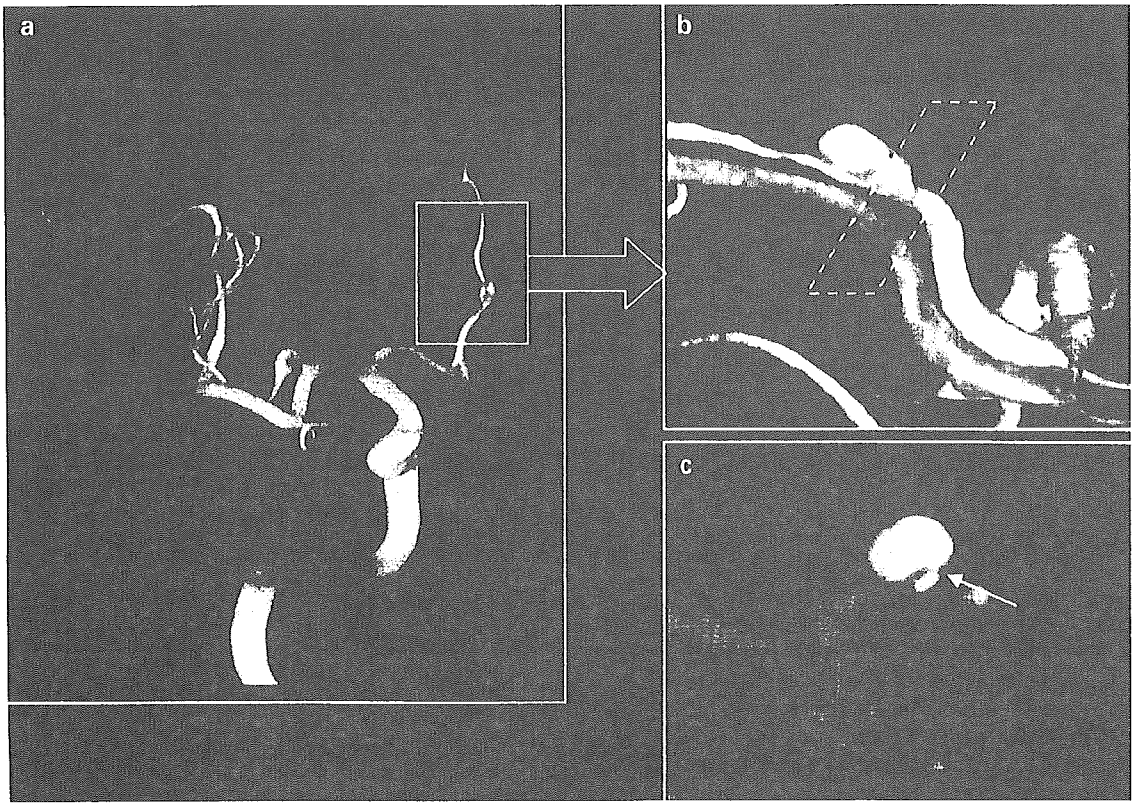

Fig. 2. Three-dimensional rotational angiography. Right carotid 3D-RA displaying aneurysmal dilatation of the right proximal A2 portion followed by segmental arterial stenosis (**a**, **b**). Cut plane (**c**) demonstrating intimal flap (arrow).

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-

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特集

血栓溶解療法

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はじめに

1995年米国NINDS（National Institute of Neurological Disorder and Stroke）rt-PA studyによって，発症3時間以内の超急性期虚血性脳血管障害に対するrecombinant tissue plasminogen activator（t-PA）静注法の有効性が証明された[1]．本薬は翌年に初の「脳血管障害治療薬」として米国食品医薬品局（FDA）で承認された．これを境に虚血性脳血管障害は「Brain attack」として超急性期治療の重要性が叫ばれるようになり，専門医療機関への超早期受診の重要性と，これに対応できる脳卒中診療体制の構築が強調されるようになった．現在，本薬は世界40カ国で承認され，欧米の主要専門学会の治療ガイドラインでも本療法が明記されている[2, 3]．また，1999年には発症6時間以内の中大脳動脈閉塞症を対象としたPROACT Ⅱ（Prolyse in Acute Cerebral Thromboembolism Ⅱ）studyによる局所線溶療法の効果も報告された[4]．2004年には，異物除去装置MERCI[5, 6]を用いた血栓除去法が米食品医薬品局（Food and Drug Administration；FDA）に承認され，今後の発展が注目されている．

本稿では，血栓溶解療法を中心に超急性期治療の現状・課題について解説する．

血栓溶解療法の理論

機能障害は生じているが不可逆的損傷には至っていない領域は虚血性ペナンブラと呼ばれ，血行再建により不可逆的損傷を免れ，機能回復も可能であるといわれている．この可逆性は脳虚血の程

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表1 血栓溶解療法の大規模無作為化比較試験の概要

	症例数	投与開始時間	用量	有効性	症候性頭蓋内出血発症率
1. SK静注法					
MAST-E(1994)[10]	270	<6時間	150万U	−	6.0%
MAST-I(1995)[11]	622	<6時間	150万U	−	17.5%
ASK(1996)[9]	340	<4時間	150万U	−	12.6%
2. t-PA静注法					
JTSG(1993)[15]	98	<6時間	20MU(duteplase)	+	8.5%
NINDS(1994)[1]	624	<3時間	0.9mg/kg(alteplase)	+	6.4%
ECASS-I(1995)[12]	620	<6時間	1.1mg/kg(alteplase)	+/−	19.8%
ECASS-II(1998)[13]	800	<6時間	0.9mg/kg(alteplase)	+/−	8.8%
ATLANTIS(1999)[14]	579	3〜5時間	0.9mg/kg(alteplase)	−	7.2%
3. 局所線溶療法					
PROACT II[4]	180	<6時間	9mg/kg(prourokinase)	+	10.0%

度と持続時間に依存する[7]．臨床的には，発症後数時間から一両日のうちに症状が劇的に改善する現象をspectacular shrinking deficit（SSD）と呼び，脳梗塞症例の10％に認められる．Minematsuら[8]は，SSDの機序として栓子の溶解に伴う脳組織の早期再灌流を推定した．また，近年の画像診断機器の発達や脳虚血病態の解明により，脳梗塞巣が完成する以前の発症3〜6時間以内に血流を再開することで脳梗塞への進展を防止あるいは軽減できることも示された．

血栓溶解療法の変遷

血栓溶解薬は開発された年代順に第1世代から第3世代に大別される．1960年代に開発された第1世代のstreptokinase（SK）やurokinase（UK）は，血栓への親和性が低く，血栓到達までに大半が失活するために，血栓溶解作用は弱い．このため大量投与が必要であるが，一方で流血中のplasminogenをplasminに変換するため，全身性の線溶状態を惹起しやすく，出血性合併症の頻度が非常に高くなった．脳卒中例に投与した試験では，死亡率がむしろ高くなり，本療法は禁忌とされた．1980年代，第2世代のt-PAやpro-urokinase（pro-UK）が開発された．これらは血栓親和性が高く，血栓溶解作用も強い．さらに，画像診断の発達によって適切な症例選択が可能となったことで，1980年代後半より本療法は再び脚光を浴び始めた．1990年代の欧米でのt-PA静注法の無作為化比較試験（randomized controlled trial；RCT）の報告を経て今日に至っている[1,2,9〜14]．最近，フィブリン親和性や酵素活性を強力にし，血中半減期を長くした第3世代の血栓溶解薬が開発され，臨床応用が検討されている．

血栓溶解療法の大規模臨床試験

1．静注法

これまでの主な大規模臨床試験の結果を示す（表1）．SK静注法は3件の試験が実施されたが，いずれもSK群で重篤な出血性合併症や早期死亡が有意に高く，すべての試験が途中で中止となった[9〜11]．1993年，Yamaguchiら[15]は世界に先駆け，超急性期脳塞栓症に対するt-PA（duteplase）静注法の多施設RCTを実施した．発症6時間以内の脳塞栓症例に対してduteplase

20MUが静脈内投与され，再開通率は有意に上昇し，1カ月目の転帰にも改善傾向が認められた．また，症候性頭蓋内出血の発症率は偽薬群と差がなかった[15]．

冒頭に述べたNINDS studyでは，3カ月後の転帰良好例は，プラセボ群21％，t-PA群34％で，t-PA群で有意に高率であった．臨床病型による有効性の差はなかった[1]．しかし，NINDSのプロトコールを用い発症3～5時間での有効性を検討したATLANTIS（Alteplase ThromboLysis for Acute Non-interventional Therapy in Ischemic Stroke）では，転帰改善効果は証明されなかった[14]．ECASS（European Cooperative Acute Stroke Study）では，1.1mg／kgのalteplase静注法で検討され，全体では90日目の転帰には明らかな差はなかったが，プロトコール違反を除いた症例で検討すると，症候の回復時間と入院期間はt-PA群で短かった．また30日目の死亡率はプロトコールに違反したt-PA群で非常に高かったことから，t-PAの使用に際しては厳密な症例選択が必要とされた[12]．この結果を踏まえてECASS Ⅱが実施された．投与量を0.9mg／kgに下げ，エントリー基準をより厳しくした．modified Rankin scale（mRS）スコア≦2の症例はプラセボ群46.0％に対し，t-PA群54.3％と有意に多かった．発症3時間以内と3～6時間での効果および出血性合併症に差はなかった[13]．これらRCTの結果を踏まえ，米国心臓病協会（AHA）などからガイドラインが示されている（表2）[2]．

2．動注法

血栓溶解薬を直接頸動脈内に投与する動注法，特にマイクロカテーテルを用い血栓溶解薬を直接血栓内に投与する局所線溶療法は1980年代後半より試みられようになった[16, 17]．PROACTはproUKを用い発症6時間以内の中大脳動脈閉塞症に対する局所線溶療法で，再開通率はproUK群58％，プラセボ群14％，転帰良好例（mRSスコア≦1）はproUK群31％に対しプラセボ群21％であった．出血性合併症は低用量ヘパリンを用いることで低くなった[18]．以上より，本格的なRCTであるPROACT Ⅱが施行された[4]．ヘパリン静注のみの群とproUKの局所投与群とを比較し，再開通率はヘパリン群18％，proUK群66％と有意差を認めた．症候性頭蓋内出血はヘパリン群2％に対し，proUK群10％と増加したが，90日目のmRSスコア≦2はproUK群で有意に高く（25％vs．40％），90日目の死亡率は同等（27％vs．25％）であった．しかし，症例数が180例と少数であるとの理由などにより，FDAの承認は得られていない．

本邦での歴史と現状

前述のように，世界初のt-PA静注法のRCTは本邦で行われた．しかし，本薬剤の特許権の問題で製造中止となり，本邦ではt-PAは未承認のまま現在に至っている．そのため大部分の施設では超急性期といえども血栓溶解療法を実施できないのが実情であった．脳神経外科を中心としたごく一部の施設では，超急性期の血栓溶解療法としてUKもしくはt-PAによる局所線溶療法が施行されてきた．本邦の全国多施設共同前向き登録調査（Japan Multicenter Stroke Investigations' Collaboration；J-MUSIC）[19]では，登録解析患者の2.1％（発症6時間以内の4.3％）に局所線溶療法が行われていた．これらの状況を踏まえ2002年よりalteplase静注法の臨床試験（Japan Alteplase Clinical Trial；J-ACT），UKによる局所線溶療法のRCT（MCA- Embolism Local

表2 t-PA静注法に関するAHAガイドラインの概要

1．対象症例：発症3時間以内の虚血性脳血管障害
2．投与方法：recombinant t-PA　0.9mg/kg（最大90mg）全体の10%を急速静注し，残りを60分間で点滴静注
3．投与前のCT：出血や早期広汎梗塞を疑わせる所見がないことを確認する
4．除外項目
　1）経口抗凝固療法中で，PT-INRが1.7以上
　2）過去48時間以内にヘパリンを使用し，APTTが延長しているもの
　3）血小板数＜10万/mm^3
　4）過去3カ月以内の脳卒中または重症頭部外傷
　5）過去14日以内の手術
　6）治療前血圧が収縮期＞185mmHg，拡張期＞110mmHg
　7）神経症候の急激な改善
　8）単独かつ軽度の神経症候（失調，感覚障害，構音障害，わずかな脱力）
　9）頭蓋内出血の既往
　10）過度の低血糖（＜50mg/dL），高血糖（＞400mg/dL）
　11）発症時のけいれん発作
　12）過去21日以内の消化管出血または尿路系出血
　13）最近の心筋梗塞
5．集中管理，治療の行える施設内で実施する
6．NIHSSスコアが23点以上の重症例は注意が必要
7．治療開始前に，予想される効果と危険性を本人，家族に十分説明すること
8．治療後24時間の集中管理
　1）高血圧時（収縮期＞180mmHg，拡張期＞105mmHg）には降圧薬の静脈内投与
　2）中心静脈ルートの確保と動脈穿刺の制限
　3）t-PA投与中および投与後30分間は膀胱カテーテル留置を避ける
　4）治療後24時間以内は胃カテーテル挿入もできるだけ避ける
　5）治療後24時間以内は抗血小板薬，抗凝固薬などの投与は行わない
9．そのほか
　1）治療後の神経学的悪化の際には，CTにより頭蓋内出血の有無を診断する
　2）出血性合併症に対しては，t-PA投与の中止，血液凝固系検査を行い，必要に応じて輸血，新鮮血漿や血小板輸血，外科的処置を行う

Fibrinolytic Intervention Trial；MELT-Japan）が開始された．

1．J-ACT

2002年より実施されたalteplase単一用量静注法のオープン試験である．NINDS試験との比較であるため，それに準じたプロトコールで行われた．発症前後にはオザグレルナトリウム，アルガトロバン，エダラボンの投与が禁止され，投与前のCT所見で中大脳動脈支配領域3分の1以上のearly CT signs（脳溝消失，基底核構造の不鮮明化など）を認めた例，NIHSSスコア4点以下およびJCS 100以上が除外項目に加えられた．急性心筋梗塞および前述のduteplase試験での投与量に基づき0.6mg／kgとされた．「3カ月後のmRSスコア≦1が33.9%以上」が有効性の，「投与36時間以内の症候性頭蓋内出血9.6%未満」が安全性のエンドポイントと定められた．

登録症例数は22施設103例で，患者背景は心原性脳塞栓症の比率が78%と高かった以外は，年齢，男女比，重症度，血圧や血糖などの指標に

NINDS試験と差はなかった．発症3カ月後のmRSスコア≦1の頻度は37％，投与開始36時間以内の症候性頭蓋内出血は5.8％と，いずれのエンドポイントも目標に到達した．なお，投薬例の死亡率は10％と，NINDS試験の17％より低率であった[20]．

2．MELT Japan

2002年始めより開始されたMELT Japanは，超急性期虚血性脳血管障害に対する局所線溶療法の有効性と安全性を，従来の一般的治療法と比較する多施設共同RCTである．年齢20～75歳の中大脳動脈塞栓症（4＜NIHSSスコア＜23），発症6時間以内に治療開始可能で，CTでearly CT signsを認めないか，レンズ核，シルビウス裂に限局する軽微な変化のみの症例を対象とした．プライマリーエンドポイントは3カ月後の転帰で，mRSスコア≦2を転帰良好と定めた．局所線溶群100例，対照群100例を目標に，現在試験継続中である[21]．

血栓溶解療法の実際

t-PA静注法は前述のとおり多数のRCTの結果により，適応症例や投与方法がAHAなどによってガイドラインとして明確化された（表2）．一方，局所線溶療法の有効性はPROACT Ⅱ以外に証明されておらず，ガイドラインも存在しない．本邦における脳卒中ガイドラインにおいてもt-PA静注法はグレードAとして推奨されている．

1．適応症例の選択

血栓溶解療法の最大の問題点は症候性頭蓋内出血の増加である．そのため症例の選択にあたってはいかに安全に行えるかがポイントとなる．t-PAによる症候性頭蓋内出血は6～17％で，最も頻度の高かったECASSを除くと6～8％である[1, 12, 13]．1997年，FDAの要請による全米57施設での389人を対象とした第4相試験 STARS（Standard Treatment with Alteplase to Reverse Stroke）研究が実施され，症候性頭蓋内出血の合併率は3.3％であった．プロトコール違反は32.6％に認められ，その内訳は発症3時間以降での投与（13.4％），24時間以内の抗血小板薬治療（6.7％），収縮期血圧＞185torr（3.3％）であった[22]．そのほか，糖尿病の合併，高齢者や重篤な臨床症候を有する例，治療前に抗血小板薬や抗凝固薬内服中であった患者は注意を要する．局所線溶療法においてもt-PA静注法同様の適応基準が使われることが多い．MELT-Japanでは，塞栓性中大脳動脈主幹部閉塞のみを対象としている．

early CT signsとは，超急性期脳虚血性変化を表すCT上の所見である．主にレンズ核の不鮮明化，insular ribbonの消失，皮髄境界の不鮮明化を指し，hyperdence MCA signを加えることもある．図1に代表的な所見を提示した．これらの所見は脳虚血の程度や重症度とも関連し，血栓溶解療法においては本所見と症候性頭蓋内出血や予後との関連が示されている[23, 24]．ECASSおよびMELT-Japan，J-ACTでは除外基準の重要な項目となっている．しかし，early CT signsの判定に際しては，判定医の熟練に加え，正しい条件下でのCT撮像が必要である．MELT-Japanでは，①コンベンショナルスキャン方式，②スライス厚8～10mm，③最適の再構成関数（フィルター），④回転速度180度／秒以下（2秒／回転以上），⑤Window幅 80以下を撮影条件としている．early CT signsの読影を誤れば重大な合併症を招く危険もあることを銘記すべきであろう．AHAのガイドラインでも専門医による判定を推奨している．

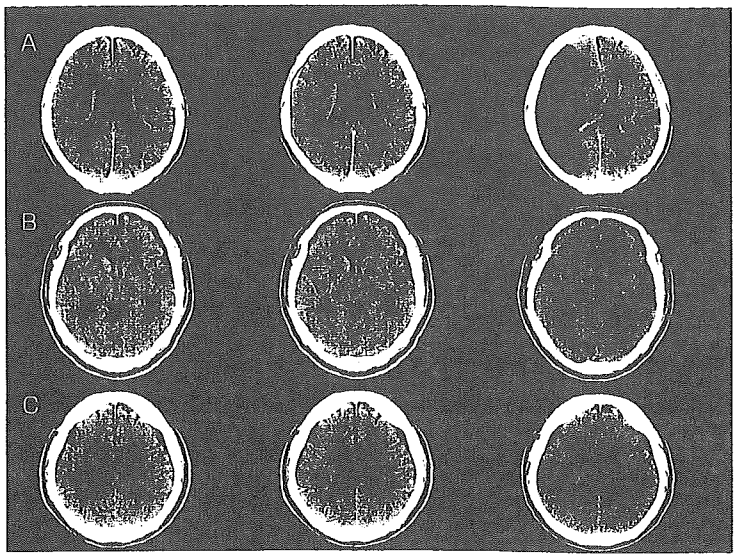

図1　early CT signsの実例

左：搬入時頭部CT
中央：early CT sings
右：入院後頭部CT
A：皮髄境界の不明瞭化
症例は74歳，男性．心房細動の既往あり．自室で倒れているところを発見された．JCS10，右共同偏視，構音障害，左片麻痺あり．搬入時頭部CTで右中大脳動脈ほぼ全域の皮髄境界の不明瞭化を認めた．第3病日のCTでは右中大脳動脈全域に低吸収域と高度脳浮腫を呈した
B：島皮質の不明瞭化，C：皮髄境界の不明瞭化
症例は78歳，男性．発作性心房細動あり．左上下肢の脱力で発症．JCS2，半側空間無視，病態失認，身体失認，左片麻痺あり．搬入時頭部CTで右島皮質の不明瞭化と，右central artery領域の皮髄境界の不明瞭化を認めた．第2病日のCTで同部位に低吸収域に認めた

2．投与方法

欧米においては，alteplase 0.9mg／kgが標準であるが，J-ACTでの投与量は前述のように0.6mg／kgである．いずれも，全体の10％を静注で投与し，残りを1時間で点滴投与する．MELT Japanでは，マイクロカテーテルにより閉塞局所で最大60万単位までのUKを注入する．この場合，血栓遠位よりの機械注入法が用いられる．図2は当施設での症例を呈示する．

3．治療後管理

t-PA静注法，局所線溶療法ともに治療後24時間まではstroke care unitなどでの厳重な集中治療管理が必要である．そのポイントは，①高血圧時（収縮期＞180mmHg，拡張期＞105mmHg）の降圧療法（静脈内投与），②中心静脈カテーテル，動脈穿刺，胃管および膀胱カテーテルの制限，③抗血小板薬，抗凝固薬投与の禁止である[4]．局所線溶療法では，再開通度の判定などが可能である．

心原性脳塞栓症では，再発が重要な予後悪化因子となる．治療24時間以降のCTにて梗塞範囲，出血性梗塞の有無を確認し，可能であればヘパリン10,000～15,000単位／dayの持続点滴静注などの抗血栓療法による再発予防対策を開始する．

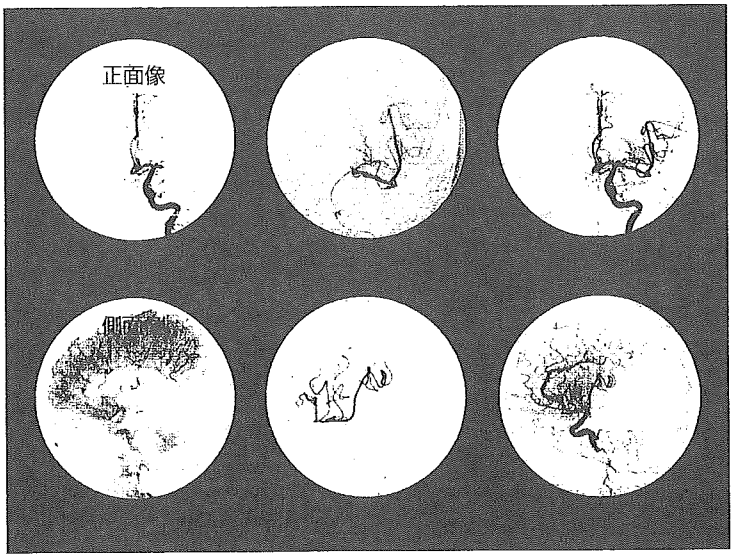

図2 局所線溶療法の実例

上段：正面像，下段：側面像
左：治療前，中央：マイクロカテーテルによる造影，右：治療後
症例は76歳女性．失語，右片麻痺で発症，搬入時JCS10，右共同偏視，全失語，右片麻痺，NIHSSスコア17点．脳血管造影で左中大脳動脈水平部に閉塞を認めた．側面像で毛細管相においてearly veinを認めた．マイクロカテーテルを閉塞血栓より末梢に留置し，UKを総量48万単位投与したところで，狭窄を残すものの再開通が得られた.術後NIHSSスコアは9点と改善した

今後の課題・展望

1．超急性期の迅速診断，診断基準

超急性期治療の成功のためには，迅速かつ正確な超急性期診断技術が必須である．実際の臨床現場では，early CT signsの的確な判定により，症候性頭蓋内出血の危険を予測し，除外できるかが重要である．近年，超急性期MRIとして，拡散強調画像（DWI）や灌流画像（PWI）の有用性が報告されているが，撮像方法や評価判定基準など標準化への課題は解決されていない．

2．新たな超急性期治療戦略の追求

t-PA静注法で再開通を得られなかった症例での治療法も課題となっている．またt-PA静注法はこれまでのところ発症3時間以内が適応であり，発症3～6時間経過した症例での治療法が課題として残っている．局所溶解療法での治療適応時間は静注法のそれより長く，発症6時間以内といわれている．PROACT ⅡやMELT Japanの結果より発症6時間以内の血栓溶解療法として確立することが期待される．一方，2004年に血管内治療による閉塞血管からの血栓除去装置MERCIがFDAで承認され，今後の展開が注目されている．また，NINDS研究とほぼ同様のプロトコールで発症6時間以内の脳梗塞6,000例を対象とした大規模RCTも開始されており，今後が注目される[25]．

3．新たな診療体制の構築

血栓溶解療法のガイドラインは安全性の確保のため，非常に厳格なものとなっている．しかし，厳格であるがゆえにt-PA投与例は米国においても脳梗塞患者全体の1～2％，中核的施設においてでも5％程度を占めるに過ぎないといわれてい