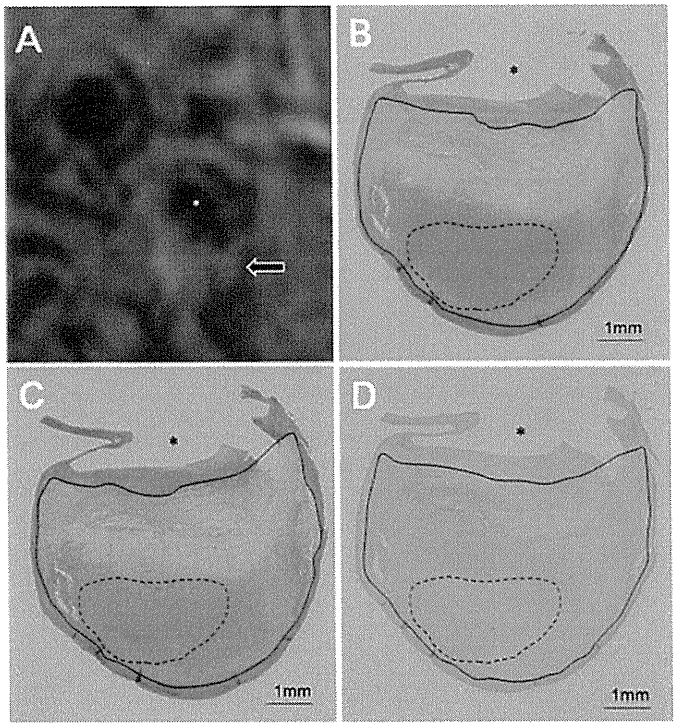

FIG. 6. An example of plaque with lower signal intensity. **A:** An MPRAGE image showing the plaque *(arrow)*. **B and C:** Photomicrographs of ICA sections show the plaque is mainly consisted of fibrous tissue and focal calcification. H & E **(B)** and Masson trichrome **(C)**. **D:** Photomicrograph showing that the plaque is only lightly stained for glycophorin A. *Asterisks* indicate the ICA lumen. The total plaque area is delineated by a *solid line* and the necrotic area by a *dotted line*. Bar = 1 mm.

pathological examination and MR imaging analysis in this study were restricted to patients with high-grade stenosis. Yet the relative risk of ipsilateral ischemia according to MPRAGE signal intensity was reported to be the highest in the moderate-stenosis group.[33] In future studies of MPRAGE, it would be better to investigate the pathological differences between patients with moderate stenosis and high signal intensity and those with moderate stenosis and lower signal intensity.

Conclusions

We demonstrated that in CA plaque with high-grade stenosis, high signal intensity on MPRAGE sequences (> 200% increase relative to signal intensity in adjacent muscle tissue) indicates larger necrotic cores and more severe degrees of IPH than lower signal intensity. We also found that IPH is closely associated with necrotic core expansion in advanced CA plaque. These results indicate that MPRAGE, a T1-weighted imaging technique, can accurately reveal plaque progression in conjunction with IPH in patients with high-grade stenosis.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: T Hishikawa, K Iihara. Acquisition of data: N Yamada, H Ishibashi-Ueda. Reviewed final version of the manuscript and approved it for submission: T Hishikawa, K Iihara, N Yamada, H Ishibashi-Ueda, S Miyamoto. Study supervision: S Miyamoto.

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Slowly progressive neuronal death associated with postischemic hyperperfusion in cortical laminar necrosis after high-flow bypass for a carotid intracavernous aneurysm

Case report

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The authors report a rare case of slowly progressive neuronal death associated with postischemic hyperperfusion in cortical laminar necrosis after radial artery/external carotid artery–middle cerebral artery bypass graft surgery for an intracavernous carotid artery aneurysm. Under barbiturate protection, a 69-year-old man underwent high-flow bypass surgery combined with carotid artery sacrifice for a symptomatic intracavernous aneurysm. The patient became restless postoperatively, and this restlessness peaked on postoperative Day (POD) 7. Diffusion-weighted and FLAIR MR images obtained on PODs 1 and 7 revealed subtle cortical hyperintensity in the temporal cortex subjected to temporary occlusion. On POD 13, ^{123}I-iomazenil (^{123}I-IMZ) SPECT clearly showed increased distribution on the early image and mildly decreased binding on the delayed image with count ratios of the affected–unaffected corresponding regions of interest of 1.23 and 0.84, respectively, suggesting postischemic hyperperfusion. This was consistent with the finding on ^{123}I-iodoamphetamine SPECT. Of note, neuronal density in the affected cortex on the delayed ^{123}I-IMZ image further decreased to the affected/unaffected ratio of 0.44 on POD 55 during the subacute stage when characteristic cortical hyperintensity on T1-weighted MR imaging, typical of cortical laminar necrosis, was emerging. The affected cortex showed marked atrophy 8 months after the operation despite complete neurological recovery. This report illustrates, for the first time, dynamic neuroradiological correlations between slowly progressive neuronal death shown by ^{123}I-IMZ SPECT and cortical laminar necrosis on MR imaging in human stroke. *(DOI: 10.3171/2009.9.JNS09345)*

Key Words • **laminar necrosis** • **iomazenil** • **bypass** • **delayed neuronal death** • **magnetic resonance imaging**

Cortical laminar necrosis is a permanent brain injury radiologically characterized by T1-weighted MR imaging–documented high-intensity cortical lesions that follow the gyral anatomy of the cerebral cortex.[7,17,19] It has been associated with hypoxia, metabolic disturbances, drugs, infections, status epilepticus, and ischemic stroke.[7,19] The neuropathological correlations, however, between neuronal loss and an emerging cortical T1 hyperintensity signal in human stroke remain unknown. Intracavernous CA aneurysms are usually treated by trapping with/without EC-IC bypass based on presumed tolerance to CA sacrifice.[6,9] Flumazenil and iomazenil are markers of central benzodiazepine receptors, part of the GABAergic complex,[2] and are ideal markers of periinfarct tissue and incomplete brain infarcts.[16] This is the first report illustrating slowly progressive neuronal death, shown by ^{123}I-IMZ, during emerging cortical laminar necrosis on MR imaging after temporary occlusion at high-flow bypass for an intracavernous CA aneurysm.

Abbreviations used in this paper: CA = carotid artery; EC-IC = extracranial-intracranial; ECA = external carotid artery; ^{123}I-IMP = ^{123}I-iodoamphetamine; ^{123}I-IMZ = ^{123}I-iomazenil; MCA = middle cerebral artery; POD = postoperative day; RA = radial artery.

Case Report

History and Examination. This 69-year-old man developed double vision and ptosis due to left oculomotor palsy. Angiograms obtained at the previous hospital showed bilateral large intracavernous CA aneurysms (Fig. 1A). After balloon test occlusion showing intolerance on temporary occlusion of the left CA, the patient was referred to our institution.

Operation. The patient's left large CA aneurysm was trapped by RA/ECA-MCA bypass grafting without causing any neurological deficit. Temporary occlusion of the inferior trunk of M_2 was performed for 52 minutes under thiopental brain protection. Postoperative MR dif-

fusion weighted imaging demonstrated no abnormality. Two months later, the patient presented with contralateral oculomotor palsy due to progressive growth of the contralateral aneurysm. He underwent virtually the same operation, except with a shorter duration of temporary occlusion (47 minutes) and except for the observation that back flow from the distal M_2 was slower and dark when the distal clip was first declamped after anastomosis, suggesting that the territory of the recipient artery had been subjected to ischemic insult due to insufficient collateral flow.

Postoperative Course. The patient awoke from anesthesia relatively soon without apparent neurological deficit. Diffusion weighted and FLAIR imaging on POD 1 showed slight cortical hyperintensity in the right temporal region (Fig. 1C and D). Angiograms obtained on POD 5 showed no opacification of the aneurysm and good bypass patency, but the patient gradually became restless. Diffusion weighted and FLAIR imaging repeated on POD 7 revealed similar findings (Fig. 1E and F). Because the signal change on diffusion weighted imaging, however, remained subtle, the cause of such MR imaging abnormality remained uncertain. Subtle Gd enhancement was noted in the temporal cortex. On POD 18, ^{123}I-IMZ SPECT showed increased distribution on the early image (15 minutes) and decreased binding on the delayed image (3 hours) in the temporal region corresponding to the hyperintensity area on diffusion weighted and FLAIR images (Fig. 2). Because early and delayed images of ^{123}I-IMZ SPECT represent the cerebral perfusion state and neuronal viability, respectively, these results clearly indicated that ischemic neuronal loss and postischemic hyperperfusion occurred as a result of ischemic insult by temporary occlusion during bypass surgery.

Chronological count ratio changes of the affected to the unaffected corresponding regions of interest on ^{123}I-IMZ and ^{123}I-IMP SPECT scans are shown in Fig. 3. In the temporal region subjected to temporary clipping, the affected/unaffected ratio on ^{123}I-IMZ scans decreased during the subacute period between PODs 18 (ratio 0.84) and 55 (ratio 0.44), and then it leveled off later (ratio 0.43 on POD 239), whereas it remained relatively constant in other regions. We did not obtain ^{123}I-IMZ SPECT scans before the operation. On ^{123}I-IMP SPECT, the affected/unaffected ratio transiently increased during PODs 13 (ratio 1.21) and 26 (ratio 1.23), and it progressively decreased on PODs 53 (ratio 0.84) and 236 (ratio 0.67) in the temporal region, although virtually no changes were noted in other areas.

Correlation of SPECT and MR Imaging Findings. Serial FLAIR images showed cortical hyperintensity, which appeared on POD 1, peaked during PODs 7 and 13, almost returned to normal on POD 56, and demonstrated atrophy in the right temporal lobe on POD 237 (Fig. 4). During transient hyperperfusion and chronic hypoperfusion stages, ^{123}I-iodoamphetamine FLAIR demonstrated marked cortical edema and chronic atrophic change of the affected region, respectively. Subtle diffusion weighted imaging hyperintensity in the affected area was shown between PODs 1 and 7 but disappeared on POD 35, despite slowly progressive neuronal death documented on ^{123}I-IMZ in the subacute phase (PODs 18–55), during which T1 cortical hyperintensity became prominent (PODs 35–56). The hyperperfusion state of the affected cortex was also confirmed by ^{123}I-IMP SPECT on POD 12. Hyperperfusion of the affected cortex gradually improved and returned to normal, as shown by ^{123}I-IMP SPECT on POD 53. Follow-up MR images showed unique chronological changes such that cortical hyperintensity of the affected cortex appeared on POD 35 and persisted at least until POD 56. Of note, cortical hyperintensity on FLAIR peaked on POD 7 and then gradually decreased in intensity and appeared almost normal on POD 56. In the late chronic stage on POD 237, cortical atrophy with secondary degeneration of the underlying subcortical white matter was noted. No hemorrhagic transformation was noted in the affected regions on CT scans throughout the observation period.

Follow-Up. The patient's cranial nerve III palsy and restlessness gradually improved and he resumed his previous lifestyle 5 months after the second surgery. Eight months after surgery, his Mini-Mental State Examination status returned to normal.

Discussion

We have presented, for the first time, dynamic neuropathological correlations between slowly progressive neuronal death during postischemic hyperperfusion, as shown on ^{123}I-IMZ and ^{123}I-IMP SPECT scans, and emerging cortical laminar necrosis, as shown on T1-weighted MR images, after RA/ECA-MCA bypass grafting for an intracavernous CA aneurysm.

Intracavernous CA aneurysms are usually treated by trapping with/without EC-IC bypass based on presumed tolerance to CA sacrifice.[9] If the CA does not tolerate the balloon test occlusion, a high-flow bypass is indicated when CA sacrifice is performed. Creation of an RA/ECA-MCA bypass graft is a common method of high-flow bypass, and the technical standards and pitfalls have been reported previously.[9,12] The incidence of ischemic complications has been reported to be ~ 10%[9] as a result of early graft occlusion and other causes, but the underlying etiological force, most of which has been considered thromboembolic, remains unproven in most cases.[6,9]

Cortical laminar necrosis is a permanent brain injury characterized on T1-weighted MR images by high-intensity cortical lesions that follow the gyral anatomy of the cerebral cortex. Histopathological and experimental animal studies have demonstrated much more vulnerability of the gray matter than white matter to ischemic necrosis due to hypoperfusion.[19] Previous studies have reported characteristic MR imaging findings of cortical laminar necrosis caused by hypoxic or ischemic brain damage.[7,19] Cortical enhancement on postcontrast T1-weighted images in the subacute stage, suggesting breakdown of the blood-brain barrier, and hyperintense cortical lesions on unenhanced T1-weighted images during the late subacute and early chronic stages were reported to be distributed in the laminae. Cortical laminar necrosis is usually reported

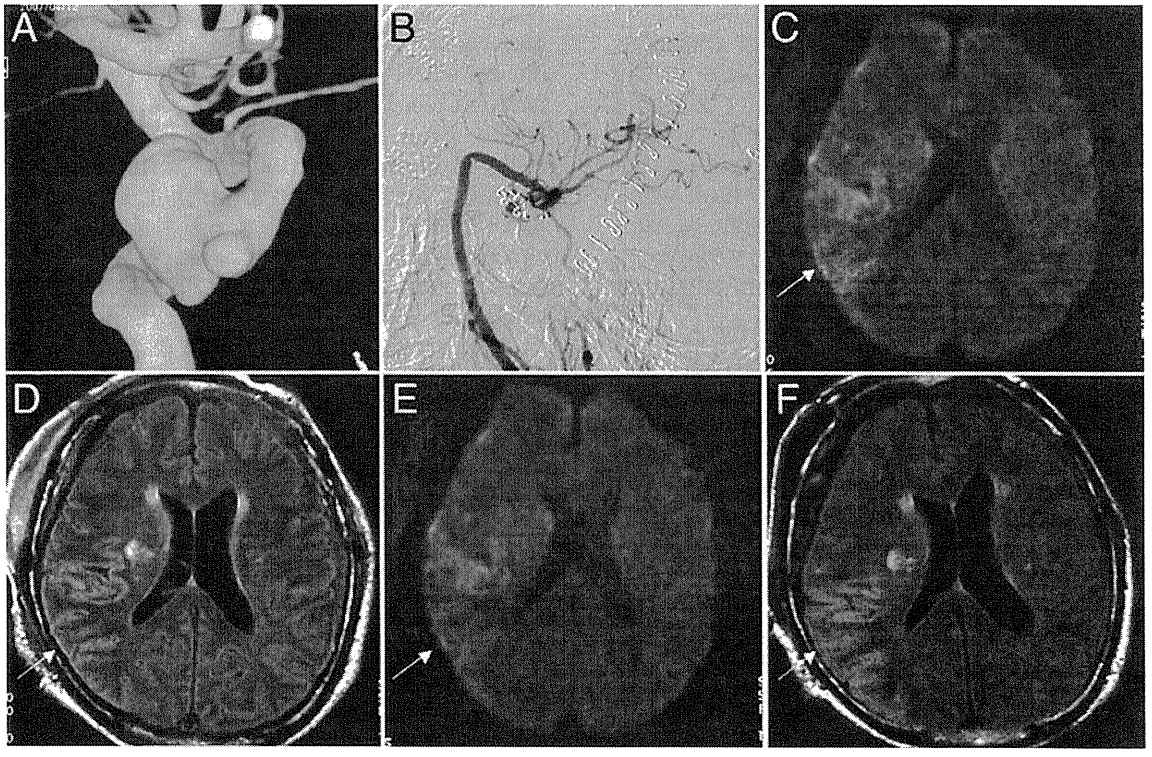

FIG. 1. **A:** Three-dimensional rotational CA angiogram showing a large intracavernous aneurysm that was treated with radial artery/ECA-MCA bypass grafting. **B:** Postoperative angiogram. **C and D:** Diffusion weighted **(C)** and FLAIR **(D)** images obtained on POD 1, showing only subtle hyperintensity in the right temporal cortex subjected to temporary clipping. **E and F:** Diffusion weighted **(E)** and FLAIR **(F)** images obtained on POD 7 when the patient became restless. Both of the hyperintensities following a gyral pattern appear slightly increased and well demarcated. *Arrows* indicate the affected region in the temporal lobe.

to be associated with volume loss of the affected cortex in the chronic stage.[20] Weiller and coworkers[20] have reported finding atrophy of the opercular cortex overlying the subcortical infarct on follow-up MR images ~ 1 year after the insult, suggesting that neuronal loss progresses over time.[13,20] In the present case we observed similar chronological changes of MR imaging signals on T1-weighted and FLAIR images and clearly illustrated the dynamic process of slowly progressive neuronal death associated with postischemic hyperperfusion in the affected cortex, where cortical hyperintensity was emerging in the subacute phase, following subtle diffusion weighted imaging–documented abnormalities in the acute phase.

Hyperperfusion is defined as a significant increase in cerebral blood flow relative to the homologous area of the contralateral hemisphere,[10] and it is known to occur after carotid endarterectomy, EC-IC bypass, and giant aneurysm clipping in patients with chronically impaired cerebrovascular reserve. Previous studies that involved the use of PET or SPECT scanning suggest that hyperperfusion may sometimes be associated with incomplete infarction or selective neuronal loss.[3,13] Flumazenil and ^{123}I-IMZ are markers of central benzodiazepine receptors, part of the GABAergic complex,[2] and ideal markers of periinfarct tissue and incomplete brain infarcts.[16] Sette et al.[16] have reported marked hyperperfusion in the affected territory in ischemic stroke, together with mildly reduced binding of ^{11}C-flumazenil in the acute stage, followed by reduced ^{11}C-flumazenil binding and reduced cerebral metabolic rates of glucose despite unaltered MR imaging findings in the subacute stage. Nakagawara and colleagues[13] have also reported using ^{123}I-IMZ SPECT in 2 patients with extensive hyperperfusion in the acute stage who exhibited reduced binding of ^{123}I-iomazenil in these areas in the chronic stage despite normal CT findings. The degree and duration of moderate ischemia in the present case was probably in the narrow range, which caused slowly progressive neuronal death without the development of frank infarction involving subcortical white matter, as reported in transient ischemia in animal models.[1] In internal carotid artery occlusive disease, selective neuronal damage was reported to occur beyond the regions of infarcts by hemodynamic ischemia in the chronic stage, as demonstrated on ^{11}C-flumazenil PET scans.[22]

The diagnostic significance of diffusion weighted imaging deserves some mention. Diffusion weighted imaging is considered an accurate predictor of the extent of infarction during the acute or early subacute phase of cerebral ischemia. Heiss et al.[4] compared the probability of cortical infarction by examining flumazenil binding on PET and diffusion weighted images in early ischemic stroke; they concluded that these modalities are comparable in predicting the probability of ischemic cortical infarction. Benzodiazepine receptor activity is a reliable marker of neuronal integrity in the cortex, but movement of water molecules in the extracellular space may be a more variable indicator of tissue damage, such that the false-positive volumes not included in the final infarct were larger for diffusion weighted imaging.[4] Subtle cortical hyperintensity on diffusion weighted imaging of the

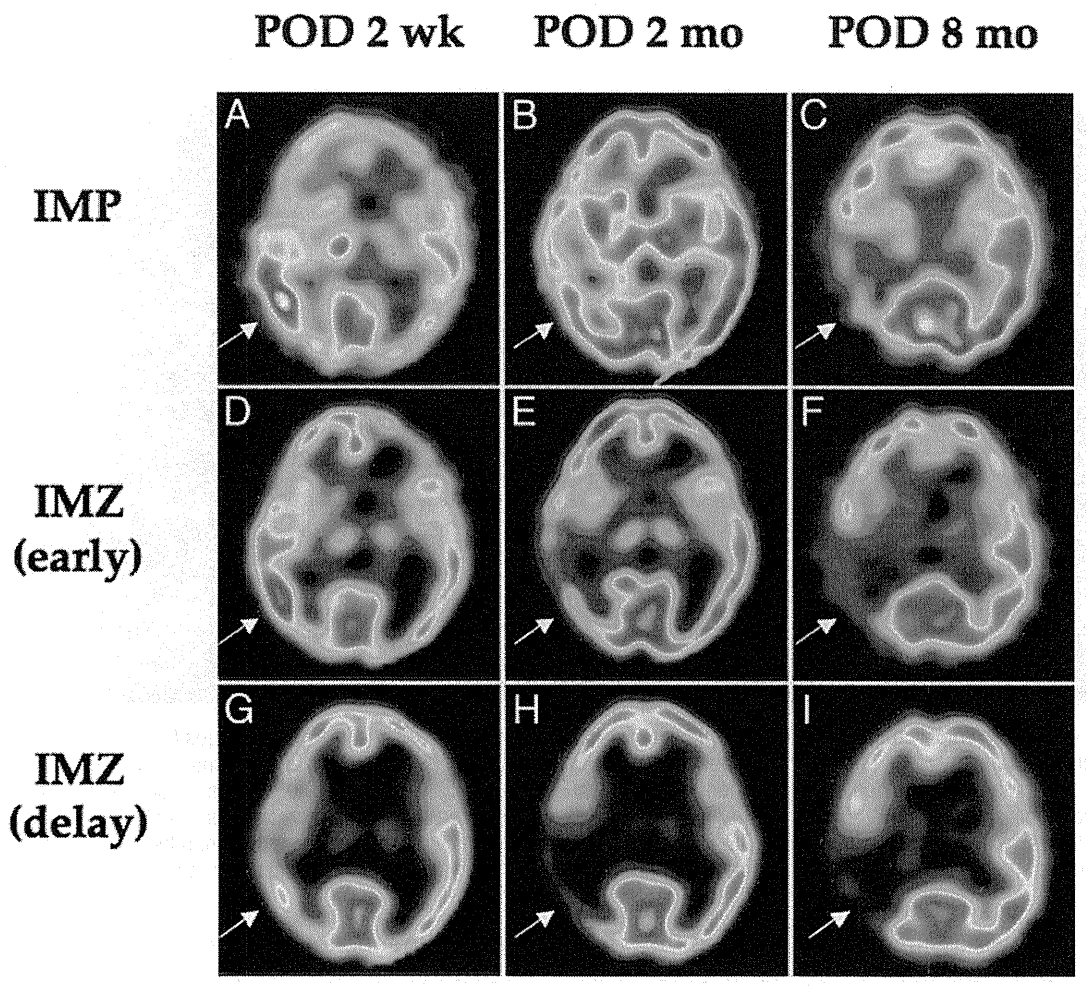

FIG. 2. Chronological changes in ^{123}I-IMP and early and delayed ^{123}I-IMZ SPECT images. Iodine-123–labeled iodoamphetamine **(A–C)** and early ^{123}I-IMZ **(D–F)** images similarly showing a transient increase in the subacute stage (POD 2 weeks [POD 2 wk; **A and D**]), followed by progressive decrease in the early and late chronic stages (POD 2 months [POD 2 mo; **B and E**] and 8 months [POD 8 mo; **C and F**]) of uptake in the affected regions. Delayed images of ^{123}I-IMZ **(G–I)** demonstrating delayed decrease of binding of the affected regions between subacute **(G)** and early chronic **(H)** stages, which levels off in the late chronic stage **(I)**. *Arrows* indicate the affected region in the temporal lobe.

affected cortex on PODs 1 and 7 in this case, as reported in global ischemia,[11] disappeared thereafter, despite ongoing neuronal loss during the subacute stage. In animal models, modest signal intensity changes on diffusion weighted imaging precede delayed neuronal necrosis after transient ischemia.[15] In the present case, however, the rate of decrease of the affected/unaffected ratio, as seen on the delayed ^{123}I-IMZ images, remained constant until POD 55 before and after the first postoperative ^{123}I-IMZ image, if the affected/unaffected ratio before surgery in

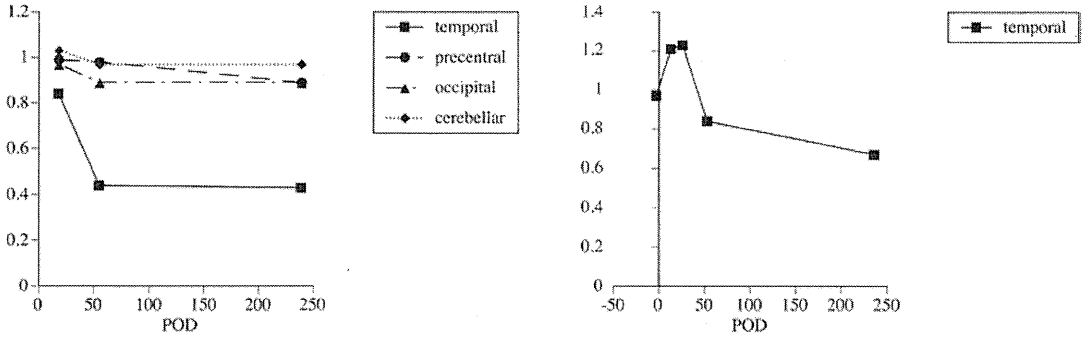

FIG. 3. Line graphs depicting chronological changes of the affected/unaffected count ratio and corresponding regions of interest on delayed ^{123}I-IMZ ***(left)*** and ^{123}I-IMP ***(right)*** SPECT images. The count ratio of the affected/unaffected corresponding regions of interest of ^{123}I-IMZ in the different areas (temporal, precentral, occipital, and cerebellar regions) are plotted against PODs. The affected/unaffected ratio of ^{123}I-IMP was plotted only for the affected temporal region.

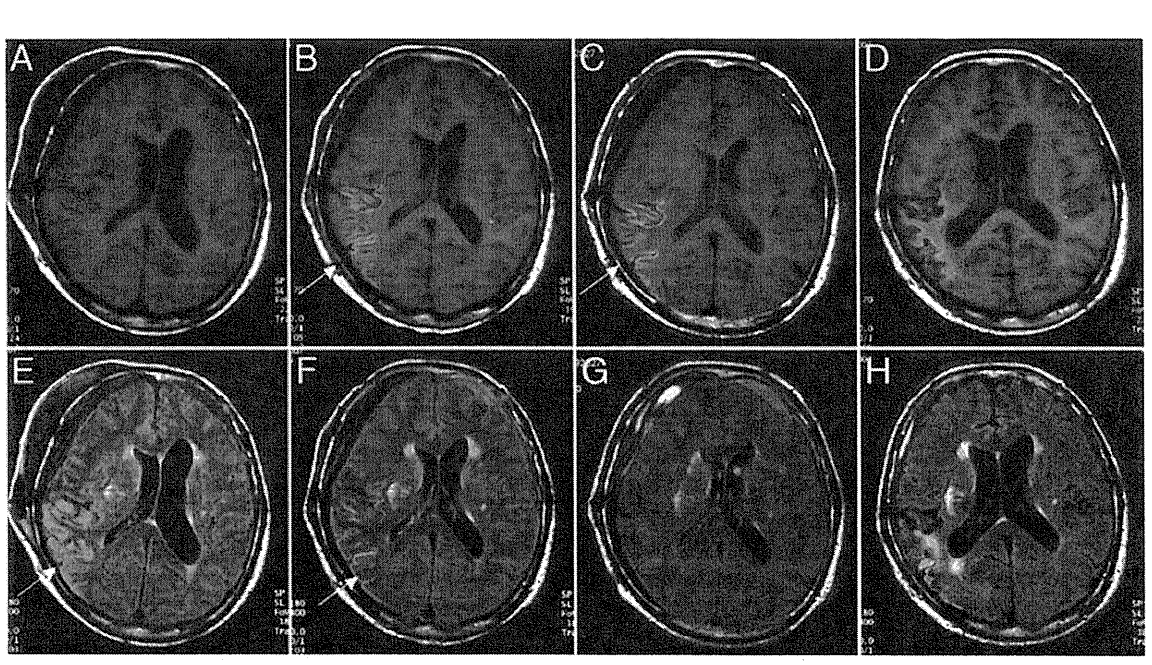

FIG. 4. Chronological changes demonstrated on follow-up MR images. Sagittal T1-weighted images (**A–D**) showing emerging cortical hyperintensity of the affected cortex between 2 weeks after surgery (POD 2 wk; **A**) and 1 month after surgery (POD 1 mo; **B**); the hyperintensity becomes more prominent at 2 months (POD 2 mo; **C**). Cortical laminar necrosis indicates atrophic change in the late chronic stage (**D**). **E–H:** On FLAIR images, cortical hyperintensity gradually decreases from 2 weeks after surgery (POS 2 wk; **E**) to 1 month after surgery (POD 1 mo; **F**) postoperatively and almost disappears by 2 months (POD 2 mo; **G**). In the late chronic stage, cortical atrophy with secondary degeneration of the underlying subcortical white matter is noted (**H**).

the affected cortex was assumed to be 1.0, as in the other areas on the first postoperative ^{123}I-IMZ image. These findings suggest that neuronal loss may not be of delayed onset, but rather slowly progressive after surgery, and diffusion weighted and ^{123}I-IMZ imaging may differ in predicting the probability of slowly progressive neuronal death in cortical laminar necrosis, depending on the interval from the moderate ischemic insult. Iodine-123–labeled IMZ SPECT is useful for examining the dynamic process of slowly progressive neuronal loss, especially in the subacute phase after moderate ischemia. Precise understanding of temporal profiles of neuronal death underlying emerging cortical laminar necrosis should require further accumulation of evidence using ^{123}I-IMZ SPECT.

Previous studies discussed the time permitted for temporary occlusion of the parent artery for aneurysm surgery, especially for an MCA bifurcation aneurysm.[8,12,14] In radial artery/ECA-MCA bypass grafting, however, the time permitted for temporary occlusion of the M_2 segment remains unclear, although the anastomotic time has been recommended to be less than 45 minutes.[12] Obviously, the time threshold for temporary occlusion may depend on multiple factors, such as the use of various neuroprotective agents,[8,14] brain temperature,[21] and extent of collateral flow and cerebrovascular reserve. During the previous 6 years, neither isolated cortical laminar necrosis nor frank infarction due to temporary occlusion had been documented in the other 21 cases treated by high-flow bypass, including 10 patients in whom temporary occlusion lasted more than 45 minutes. In the present case, extremely slow backflow from the distal side of the clamped artery was a key intraoperative finding, underlying the development of slowly progressive neuronal death. Although previous studies have reported possible preventative measures of ischemic complications related to temporary occlusion, such as excimer laser–assisted nonocclusive anastomosis,[18] the development of small intravascular shunts,[12] and double insurance bypass,[5] there are no widely accepted methods for this purpose.

Conclusions

We have discussed a rare case of slowly progressive neuronal death during postischemic hyperperfusion in cortical laminar necrosis associated with radial artery/ECA-MCA bypass grafting for intracavernous CA aneurysms. We have illustrated the diagnostic importance using of ^{123}I-IMZ SPECT in the subacute phase before emerging characteristic MR imaging findings. Moderate ischemia during temporary occlusion due to poor collateral flow may cause this rare ischemic complication.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Clinical Features and Functional Outcome of Stroke After Transient Ischemic Attack

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Background: Transient ischemic attacks (TIAs) greatly increase the risk of stroke, but few reports have examined subsequent stroke in patients with history of TIA. *Methods:* This retrospective, hospital-based study included 506 consecutive patients with acute ischemic stroke who were admitted to our hospital. The clinical features and prognosis were compared between patients with and without TIA. Multiple logistic regression analysis was also performed to identify predictors for poor outcome. *Results:* Of 506 patients, 114 (22.5%) had a history of TIA. Compared to patients without previous TIAs (non-TIA group), patients with previous TIAs (TIA group) were significantly more likely to have hypertension (76.3% vs 64.3%; $P = .016$), dyslipidemia (57.0% vs 41.1%; $P = .003$), chronic kidney disease (28.1% *v* 15.1%; $P = .001$), intracranial major artery stenosis (51.8% vs 36.2%; $P = .018$), and large artery atherothrombosis (43.9% vs 28.3%; $P = .002$). There was no difference in the previous use of antithrombotic medications between the groups (36.0% vs 35.2%; $P = .881$). Although stroke severity on admission was similar, poor functional outcome (modified Rankin Scale score ≥4) was significantly more frequent in the TIA group, and history of TIA was an independent determinant of unfavorable outcome on multiple logistic regression analysis (odds ratio 1.46; 95% confidence interval 1.02–2.10; $P = .041$). *Conclusions:* Atherothrombotic stroke with concomitant vascular risk factors were more frequent in the stroke patients with than without previous TIA. Antithrombotic therapy was conducted only in one-third of the patients even after TIA. The stroke patients with history of TIA were at great risk of disabling stroke. Key **Words:** Acute stroke—clinical features—functional outcome—transient ischemic attack.

Transient ischemic attack (TIA) is a widely recognized warning sign for subsequent stroke. However, because the symptoms of this "warning event" disappear in a short time, even without any treatment, they tend to be disregarded or ignored by both patients and their families. For the same reason, even general physicians sometimes attach low priority to such symptoms. However, many clinical studies have shown that patients are at great risk immediately after TIA, and the short-term risk of stroke has been a focus of attention.[1-9] There has been much research showing the need for urgent assessment and treatment of TIA,[10,11] but detailed reports about the status of acute ischemic stroke in patients with a history of TIA are limited. Clarification of the effect of TIA on the subsequent course of recurrent stroke may be extremely useful information in considering strategies for preventing recurrent stroke after TIA. Therefore, a hospital-based study to investigate clinical features

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and functional outcomes of acute ischemic stroke patients with a history of TIA compared to those without a history of TIA was conducted.

Materials and Methods

Subjects

A retrospective, hospital-based study was conducted involving 515 consecutive acute ischemic stroke patients hospitalized in the Department of Neurology at Tokyo Women's Medical University Hospital between April 2005 and March 2010. Eligible patients were those within 1 week of the onset of their first symptomatic ischemic stroke and who were independent in activities of daily living with a modified Rankin Scale (mRS) score ≤2 before the stroke. After excluding 9 patients because they were lost to follow-up or moved out of the region, 506 patients were included in the analysis. These stroke patients were divided into 2 groups: 1 with history of TIA (TIA group) and 1 without such history (non-TIA group), and their respective clinical features and outcomes were compared.

Protocol

The ethics committee of our institution approved the protocol of this study. Data were collected from a computerized observational database, imaging data, and medical records of other hospitals or private practitioners. Our clinic keeps a prospective registry of all consecutive patients. We used a standardized case report form and abstracted a number of demographic and clinical variables including date of the event, medical history, risk factors for stroke, previous medications, previous TIA, physiologic, examination findings and neurologic symptoms. We also documented the results of all diagnostic tests and details of treatment performed during hospitalization. The person imputing data was blinded to the purpose of this study.

At the time of hospitalization, demographic characteristics, medication history, risk factors for stroke, and history of TIA were thoroughly investigated, and a blood sample, chest radiograph, electrocardiogram (ECG), and computed tomographic (CT) scan of the head were obtained. A magnetic resonance imaging (MRI) scan or magnetic resonance angiographic (MRA) scan of the head was performed in 501 patients, after excluding those with cardiac pacemakers or other contraindications. These were all performed within 24 hours of hospital admission. The information was also collected from private practitioners and other hospitals by fax or mail. All strokes were diagnosed by stroke neurologists based on neurologic observations and MRI or CT findings. The vascular territories of ischemia were classified as (1) left anterior circulation, (2) right anterior circulation, (3) posterior circulation, or (4) multiple. Assessments were made for severity of the event according to the National Institute of Health Stroke Scale (NIHSS); NIHSS scores range from 0 to 42, with higher values reflecting more severe neurologic deficits.

Ischemic stroke was defined as an episode of focal neurologic deficits with acute onset lasting >24 hours (or lasting <24 hours with imaging evidence of stroke corresponding with current symptoms). TIA was defined as an acute loss of cerebral or ocular function lasting <24 hours and without corresponding imaging evidence of an ischemic lesion. In accordance with the recommendations of international guidelines,[12] all information obtained from the patients, relatives, caregivers, and medical records of our hospital, other hospitals, or private practitioners were evaluated, and a final diagnosis of TIA was based on the consensus agreement of 2 or more board-certified stroke neurologists. Patients with disagreements of the diagnosis of TIA were excluded from this study. Patients who had not undergone brain imaging during or shortly after TIA were also excluded.

Diagnostic tests during hospitalization included carotid artery ultrasound, transthoracic cardiac ultrasound, and Holter ECG in all patients, plus transcranial Doppler ultrasound, transesophageal echocardiography, 3-dimensional CT angiography (CTA), digital subtraction angiography, and cerebral blood flow single-photon emission computed tomography in some patients when clinically indicated. In patients in whom findings suggesting a right-to-left shunt were confirmed, the presence or absence of venous thrombi was checked with leg vein ultrasound or full body contrast CT or magnetic resonance venography. All cardiac evaluations were conducted by trained cardiologists. The treatment regimen for each patient was determined in accordance with the international consensus by a neurologist with experience treating neurovascular disease.

Stroke-related disability/handicap was assessed by an attending doctor of our hospital with the mRS at the 3-month follow-up. When the patients could not attend the follow-up appointment, we contacted their family members or the staff of rehabilitation center or nursing home by phone. Patients who had died by 3 months were scored as mRS score 6. Poor functional outcome was defined as an mRS score ≥4.

Baseline Risk Factors

Body mass index was measured as kg/m^2. Hypertensive patients were defined as those who were receiving antihypertensive treatment at the time of the event, or those with continuing high values of systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg after >1 week had passed since the event. Patients with diabetes mellitus were defined as those who had previously been diagnosed with type 1 or 2 diabetes, or those with fasting blood glucose ≥126 mg/dL

or blood glucose ≥200 mg/dL on 2 random measurements. Patients with dyslipidemia were defined as those who had been receiving lipid-lowering treatment at the time of the event, or those with serum low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol ≤40 mg/dL, or serum triglycerides ≥150 mg/dL. The estimated glomerular filtration rate (eGFR) was calculated from the modification of diet in renal disease formula by the Japanese coefficient; chronic kidney disease (CKD) was defined as an eGFR <60 mL/min/1.73 m^2. Smoking status was determined based on whether or not the patient was a current smoker. Intracranial arterial stenosis ≥50% on MRA, CTA, or angiograms was considered significant. Carotid artery ultrasounds were read by appropriately trained neurologists, and stenosis ≥50% was defined as significant extracranial arterial stenosis. Patients with either significant intra- or extracranial artery stenosis were considered to have major artery lesions. The history of ischemic heart disease (IHD; myocardial infarction or angina pectoris) and peripheral arterial disease (PAD) was recorded, and any kind of medical condition in the past was taken to be a previous condition. Atrial fibrillation (AF) was judged based on 2 or more ECGs taken before or during hospitalization. All patients were invariably under continuous ECG monitoring during the acute phase.

Stroke Subtypes

Subtypes classified by etiology were large artery atherosclerosis (LAA), cardioembolism (CE), small-vessel occlusion (SV), other cause (OC), or undetermined cause (UND), in conformity with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[13] Stroke subtype was assigned to each patient by pairs of investigators during hospitalization. In cases of discrepancy, the patient records were reviewed by a few senior investigators, and the final categorization was based on their consensus agreement.

Statistical Analysis

Analyses were performed with SPSS software (v 11.0; SPSS Inc., Chicago, IL). Statistical significance for intergroup differences was assessed by the Chi-square test for categorical variables and the Student *t* or Mann–Whitney *U* tests were used for continuous variables. To identify predictors for poor outcome, we performed multiple logistic regression analysis based on a forward stepwise method including all variables with *P* values <.25 in univariate analysis as follows: history of TIA, SBP ≥140 mm Hg, DBP ≥90 mm Hg, major artery stenosis, history of PAD, AF, and NIHSS score at admission. Because of their clinical relevance and potential importance, age ≥75 years, other vascular risk factors (diabetes mellitus, dyslipidemia, CKD, and smoking), history of IHD, previous antithrombotic therapy, and thrombolytic therapy were retained in the final regression model. Stroke subtypes were excluded from the model because LAA and CE have multicolinearities with major artery stenosis and AF, respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In all analyses, $P < .05$ was considered significant (2-sided test).

Results

Clinical Features

The subjects in this study were 506 acute stroke patients (mean age 68.5 years; 63.6% males). All patients were of Asian descent. Of 506 patients, 114 (22.5%) had a history of TIA. Table 1 shows a comparison of patient characteristics between patients with history of TIA and those without history of TIA. There were no differences between the groups in age, sex, or length of hospitalization. In a comparison of vascular risk factors, the TIA group had significantly higher percentages for hypertension (76.3% vs 64.3%; $P = .016$), dyslipidemia (57.0% vs 41.1%; $P = .003$), and CKD (28.1% vs 15.1%; $P = .001$). There were no differences with regard to diabetes mellitus or current smoking. Patients in the TIA group had a greater number of vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, CKD, and current smoking) than those in the non-TIA group (mean 2.2 vs 1.7; $P < .001$). The TIA group also had significantly more patients with intracranial major artery stenosis (51.8% vs 36.2%; $P = .003$) and a history of PAD (8.8% vs 3.1%; $P = .009$). The prevalence of AF was nearly equal (30.3% vs 27.3%; $P = .476$).

With regard to stroke subtypes, the percentage of LAA was found to be significantly higher in the TIA group than in the non-TIA group (43.9% vs 28.3%; $P = .002$), while there were no differences in the percentages of CE or SV between the groups. Among patients in whom the subtype was OC, 1 of the patients with antiphospholipid syndrome had a history of TIA.

There were no differences between the 2 groups in the distribution of vascular territories of ischemia, in the percentage of patients who had been receiving antithrombotic therapy before the stroke (36.0% vs 35.2%; $P = .881$), or in the median NIHSS score at the time of hospitalization (8 vs 8; $P = .321$).

Functional Outcome

Figure 1 and Table 2 show the patients' status 3 months after stroke onset. Of 506 patients, 153 (30.2%) had a poor functional outcome and 10 died. In the TIA group, 44 of 114 patients (38.6%) had a poor outcome, significantly higher than the 109 of 392 patients (27.8%) in the non-TIA group ($P = .027$). An analysis by subtype showed that 50 of 161 patients (31.1%) with LAA, 29 of 161 (18.0%) with CE, and 19 of 98 (19.4%) with SV had history of TIA, and with all subtypes, the percentage of patients with a poor prognosis was higher in the TIA group than

Table 1. *Clinical characteristics of patients with and without a history of transient ischemic attack*

	All	TIA group	Non-TIA group	*P* value (TIA *v* non-TIA)
No. of patients	506	114	392	
Age, y, mean (SD)	68.5 (14.3)	69.6 (12.2)	68.2 (14.9)	.368
Male	322 (63.6%)	78 (68.4%)	244 (62.2%)	.228
Length of hospital stay, days, mean (SD)	28.5 (19.2)	29.6 (17.6)	28.2 (19.7)	.485
Body mass index, kg/m^2, mean (SD)	23.3 (3.5)	23.6 (3.6)	23.2 (3.5)	.350
Vascular risk factors				
Hypertension	339 (67.0%)	87 (76.3%)	252 (64.3%)	.016
Diabetes mellitus	193 (38.1%)	52 (45.6%)	141 (36.0%)	.062
Dyslipidemia	226 (44.7%)	65 (57.0%)	161 (41.1%)	.003
Chronic kidney disease	91 (18.0%)	32 (28.1%)	59 (15.1%)	.001
Current smoking	119 (23.5%)	32 (28.1%)	87 (22.2%)	.193
No. of vascular risk factors, mean (SD)	1.8 (1.1)	2.2 (1.1)	1.7 (1.1)	<.001
SBP, mm Hg, mean (SD)	147.3 (26.4)	152.4 (26.5)	145.8 (26.3)	.019
DBP, mm Hg, mean (SD)	82.3 (15.2)	84.5 (15.6)	81.7 (15.1)	.086
Major artery stenosis	201 (39.7%)	59 (51.8%)	142 (36.2%)	.003
Intracranial	134 (26.5%)	40 (35.1%)	94 (24.0%)	.018
Extracranial	82 (16.2%)	23 (20.2%)	59 (15.1%)	.191
History of ischemic heart disease	101 (20.0%)	27 (23.7%)	74 (18.9%)	.258
History of peripheral artery disease	22 (4.3%)	10 (8.8%)	12 (3.1%)	.009
Atrial fibrillation	142 (28.1%)	35 (30.7%)	107 (27.3%)	.476
Stroke subtype				
Large-artery atherosclerosis	161 (31.8%)	50 (43.9%)	111 (28.3%)	.002
Cardioembolism	161 (31.8%)	29 (25.4%)	132 (33.7%)	.097
Small-vessel occlusion	98 (19.4%)	19 (16.7%)	79 (20.2%)	.407
Other	25 (4.9%)	1 (0.9%)	24 (6.1%)	.023
Undetermined	61 (12.1%)	15 (13.2%)	46 (11.7%)	.681
Vascular territory of ischemia				
Left anterior	174 (%)	42 (36.8%)	132 (33.7%)	.531
Right anterior	170 (%)	41 (36.0%)	129 (32.9%)	.543
Posterior	150 (%)	29 (25.4%)	121 (30.9%)	.264
Multiple lesions	12 (%)	2 (1.8%)	10 (2.6%)	.623
Previous antithrombotic therapy	179 (35.4%)	41 (36.0%)	138 (35.2%)	.881
Antiplatelet therapy	144 (28.5%)	37 (32.5%)	107 (27.3%)	.283
Anticoagulant therapy	46 (9.1%)	8 (7.0%)	38 (9.7%)	.382
NIHSS, median (IQR)	8 (5-12)	8 (6-12)	8 (5-12)	.321

Abbreviations: DBP, diastolic blood pressure; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack.

Unless otherwise indicated, figures expressed as n (%).

in the non-TIA group, although the difference was not significant. The results of multivariate analysis showed that history of TIA was an independent predictor of poor outcome at 3 months (OR 1.46; 95% CI 1.02-2.10; $P = .041$; Table 3). Other significant factors were major artery stenosis (OR 1.63; 95% CI 1.15-2.33; $P = .007$), AF (OR 1.52; 95% CI 1.04-2.23; $P = 0.03$), and NIHSS score on admission (OR 1.72; 95% CI 1.56-1.93; $P < .001$).

Discussion

In the present study, atherothrombotic stroke with concomitant vascular risk factors was more frequent in stroke patients with a history of TIA than in those without a history of TIA. In addition, although the NIHSS score at the time of hospitalization was nearly equal in the 2 groups, there were significantly more patients with poor outcome in the TIA group. On multivariate analysis, a history of TIA was found to be an independent predictor of poor outcome.

In our hospital-based study, the percentage of stroke patients who had experienced TIA was 22.5% (114/506).

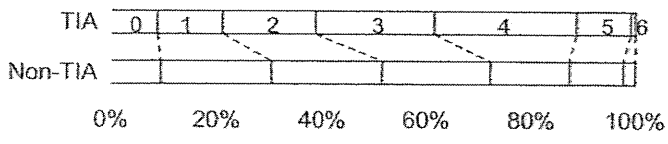

Figure 1. *Distribution of modified Rankin Scale scores 3 months after stroke onset.*

Table 2. *Percentage of poor outcomes at 3 months, overall and by subtype*

	TIA	Non-TIA	*P* value
All (n = 506)			
No. of patients	114	392	
mRS, median (IQR)	3 (2-4)	2 (1-4)	
mRS ≥4	44 (38.6%)	109 (27.8%)	.027
mRS 6	1 (0.9%)	9 (2.3%)	.338
Large artery atherosclerosis (n = 161)			
No. of patients	50	111	
mRS ≥4	24 (48.0%)	39 (35.1%)	.122
Cardioembolism (n = 161)			
No. of patients	29	132	
mRS ≥4	13 (44.8%)	49 (37.1%)	.44
Small-vessel disease (n = 98)			
No. of patients	19	79	
mRS ≥4	2 (10.5%)	3 (3.8%)	.231

Abbreviations: IQR, interquartile range; mRS, modified Rankin Scale.

Unless otherwise indicated, figures expressed as n (%).

Table 3. *Multiple logistic regression analysis for poor outcome*

	OR (95% CI)	*P* value
History of TIA	1.46 (1.02-2.10)	.041
Age ≥75 y	1.26 (0.99-1.77)	.18
SBP ≥140 or DBP ≥90 mm Hg	1.20 (0.86-1.68)	.29
Diabetes mellitus	1.01 (0.79-1.49)	.60
Dyslipidemia	0.98 (0.70-1.37)	.92
Chronic kidney disease	0.94 (0.63-1.39)	.76
Current smoking	1.10 (0.75-1.61)	.61
Major artery stenosis	1.63 (1.15-2.33)	.007
History of ischemic heart disease	0.79 (0.50-1.21)	.28
History of peripheral artery disease	1.49 (0.76-2.91)	.24
Atrial fibrillation	1.52 (1.04-2.23)	.03
Prior antithrombotic therapy	1.08 (0.74-1.58)	.66
NIHSS score on admission	1.72 (1.56-1.93)	<.001
Thrombolytic therapy	0.63 (0.16-2.05)	.50

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure; TIA, transient ischemic attack.

This percentage was particularly high in LAA patients (31.1%). In previous reports, the prevalence of a previous TIA among patients who presented with stroke has been reported to be wide-ranging. The percentage varies, depending on such factors as how TIA is defined, which stroke subtypes are evaluated, and whether the study is population- or hospital-based.[14,15] In the population-based Northern Manhattan Stroke study, the prevalence of TIAs among those who presented with first ischemic stroke was 8.7%.[16] Studies that have included patients with previous stroke, such as the Harvard Stroke Registry and National Institute of Neurological Disorders and Stroke databank, have reported higher rates of TIAs—as high as 50% among those with atherothrombotic stroke.[17,18] However, because TIA was defined without consideration of the presence or absence of imaging findings of stroke, the percentage may be overestimated when a new definition is used.

The percentages of etiologic subtypes among all stroke patients differ greatly by country and race.[19-22] In our study, LAA and CE accounted for about one-third of patients, which is similar to a past report in Japan.[23] Purroy et al[24] investigated the risk of recurrence after TIA with respect to etiologic subtype and reported that the stroke risk was higher in LAA patients than in other subtypes. We also found that there were many LAA stroke patients after TIA, and obtained new findings that their functional outcome was poorer than that of patients who had not experienced TIA. Differences were not significant in an analysis by subtype, but there tended to be more patients with poor outcomes in all subtypes. However, these findings seem to be quite contrary to the conception of "ischemic tolerance." In a number of animal models, reduced impact of ischemia after an initial ischemic insult—ischemic preconditioning—has been shown.[25] The degree of protection from infarction is supposed to be greater with longer duration and greater distribution or severity of the initial ischemia and dependent on the duration between the initial and subsequent injuries. Several clinical studies also have suggested that ischemic strokes are less severe in patients with previous TIA,[26-29] but each has limitations inherent in observational studies. That is, location, duration, and etiology of previous TIA are not always reliable from clinical history and there is no real measure of "dose" or severity of the ischemia. In addition, TIA often precipitates treatment with prophylactic medications, and these medications may impact outcomes. Considering that the condition of artificial ischemia in animal models is different from that of clinical TIA based on multiple vascular risk factors, it may be hard to entirely reconcile with animal studies.

This study had limitations. First, it was a retrospective study. We conducted an analysis based on a computerized database created during the period of patient hospitalization and postdischarge follow-up. Second, because it was a hospital-based study, the characteristics of the cohort may have differed from those of the general community population. These limitations might affect our findings. This study did not investigate the $ABCD^2$ score, length of TIA, territory of TIA, and the time after TIA until stroke recurrence. With regard to multivariate analysis,

prestroke activities of daily living and infectious complications during hospitalization could be confounding factors for poor functional outcome, but the accurate information of these factors was unavailable retrospectively. As to the prestroke activities of daily living, we investigated whether the activity of the patients' daily living had been independent (mRS ≤2) or not. We should have included these factors in the model for precise analysis. It is generally accepted that diabetes[30-32] and CKD[33,34] are associated with poor functional outcome in ischemic stroke, but these factors were not significantly associated with poor functional outcome in our study. The discrepancy might be related to the small sample size and imperfect multivariate model. We included previously diagnosed patients in defining vascular risk factors, and not a few of them had been treated before stroke. We did not take the condition of previous treatment into account, and it potentially affected the results. The subjects of our study seemed to be younger than those of previous reports that revealed a poor outcome in stroke patients with diabetes[30-32] or CKD[33,34]; therefore, the younger age of our subjects might also affect the results. Although additional studies are needed to examine our findings, our study may provide important and useful information in considering stroke prevention strategies in patients with TIA.

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1．急性脳血管症候群の概念と意義

内山真一郎*
うちやましんいちろう

- 一過性脳虚血発作（TIA）は発症直後ほど脳梗塞を続発する危険性が高いので救急疾患として対処する必要がある．
- TIA と急性虚血性脳卒中（AIS）は同一スペクトラム上にある病態であり，持続時間で区別するのは意味がない．
- 急性脳血管症候群（ACVS）は TIA と AIS を包括する概念であり，不安定狭心症と急性心筋梗塞を包括する急性冠症候群（ACS）に相当する．
- TIA は ACVS として 24 時間・365 日対応できる TIA クリニックのような救急診療体制の整備が必要である．
- ACVS としての TIA への救急対応は AIS の発症を水際で防止することにより大きな医療経済効果が期待できる．

Key Words　急性脳血管症候群，一過性脳虚血発作，急性虚血性脳卒中，TIA クリニック，国際登録観察研究

一過性脳虚血発作（transient ischemic attack：TIA）は脳梗塞の前兆として重要な病態であるが，TIA は発症直後ほど脳梗塞を続発するリスクが高い（**図 1**）[1]ため，TIA を救急疾患としてとらえ，早期診断と早期治療を行うことの重要性が強調されるようになった．

本稿では，TIA を包括する新しいコンセプトを提唱し，その意義について述べてみたい．

□ TIA の診断基準の変遷

TIA は，米国の National Institute of Neurological Disorders and Stroke（NINDS）の分類第Ⅲ版（NINDS-Ⅲ）[2]をはじめとする各国の診断基準において，24 時間以内に消失する局所的な脳または網膜の虚血症状と定義されてきた[3]が，米国の研究作業部会（TIA Working Group）が 2002 年に TIA の新しい診断基準を提唱した[4]．そのときの定義によれば，「TIA は局所的な脳または網膜の虚血によって生じる神経機能障害の一過性エピソードであり，臨床徴候の典型的な持続時間は 1 時間以内であり，急性脳梗塞の証拠がないもの」としている．この定義はその後行われた多くの大規模な臨床試験の試験計画に採用された．

しかしながら，同作業部会員達は，2009 年に米国心臓協会（American Heart Association：AHA）と米国脳卒中協会（American Stroke Association：ASA）による学術声明（Scientific Statement）として，再度新たな診断基準を発表した[5]．この診断基準では，「TIA は，急性脳梗塞を伴わない，局所的な脳，脊髄，または網膜の虚血によって生じる神経機能障害の一過性エピソードである」と定義している．すなわち，2002 年からの変更点としては，局所虚血症状を生じる部位として脊髄が加えられたことと，1 時間以内という持続時間の記載がなくなったことが挙げられる．

□ 新たな疾患概念の提唱

前述したように，TIA の新定義が盛んに議論されているが，救急疾患としての TIA と急性虚血性脳卒中（acute ischemic stroke：AIS）は同一スペクトラム上にあり，両者を持続時間のみで区別するのは意味がないと考える．実際，Easton ら[5]によれば，10 件の MRI 研究から得られたデータを統合解析したところ，神経症状の持続時間と MRI 拡散強調画像の陽性率との関係は連続的であり，特定の持続時間で区切ることができなかったという（**図 2**）．

冠動脈疾患の分野では，不安定狭心症と急性心筋梗塞を急性冠症候群（acute coronary syn-

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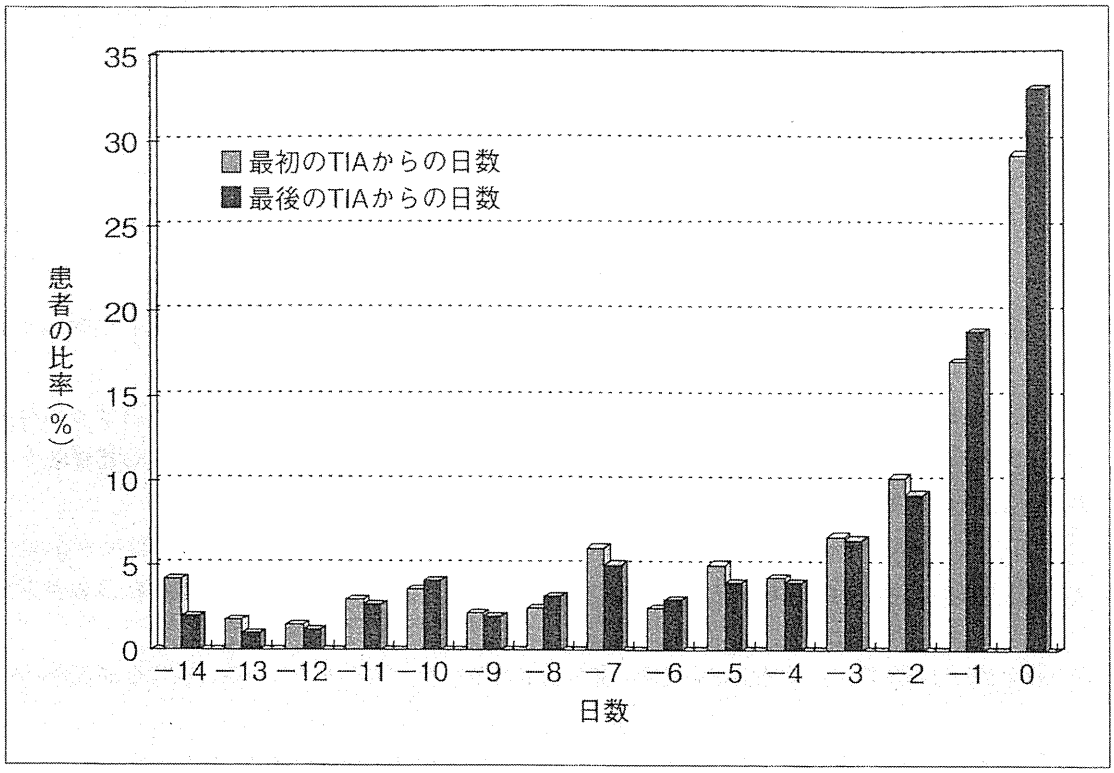

図1　TIAを発症してから2週間以内の脳卒中のリスク
(Rothwell PM, Warlow CP：Neurology 64：817-820, 2005[1]より引用改変)

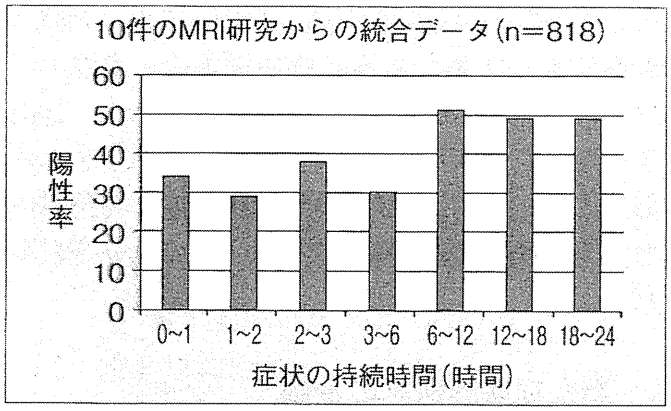

図2　神経症状の持続時間と拡散強調画像の陽性率
(Easton JD, et al.：Stroke 40：2276-2293, 2009[5]より引用改変)

drome：ACS）と総称して救急診療体制を整備することにより救命率が飛躍的に向上したという好例がある．そこで，筆者らは急性期のTIAと虚血性脳卒中を包括する新しい臨床概念として急性脳血管症候群（acute cerebrovascular syndrome：ACVS）という用語を提唱している（図3）．ACVSにはTIAとAISが包括される．可逆的な脳虚血であればTIAであり，不可逆的な脳虚血であればAISである．このようなTIAとAISの関係は，ACSに包括される，可逆的な心筋虚血である不安定狭心症と，不可逆的な心筋虚血である急性心筋梗塞の関係に対応する．

□ 急性脳血管症候群患者への救急対応の効果

ACVSは救急疾患であり，24時間・365日診療するTIAクリニックのような救急診療体制の整備が望まれている．

英国で行われたEXPRESS研究[6]によれば，一次診療医はTIAが疑われたらファックスで専門医に紹介し，TIAを緊急入院させなければいけないとは考えてもいなかったが，TIAが疑われたらただちにTIAクリニックの専門医に直接送る体制に改めたところ，TIA発症後3ヵ月間の脳梗塞発症率は10%以上から4%に激減したという（図4）．

また，フランスで行われたSOS-TIA研究[7]では，9時から17時までを専門看護師がカバーし，17時から9時までと週末を脳卒中神経内科医がカバーすることにより，24時間・365日ホットラインでTIA患者に対応するTIAクリニック体

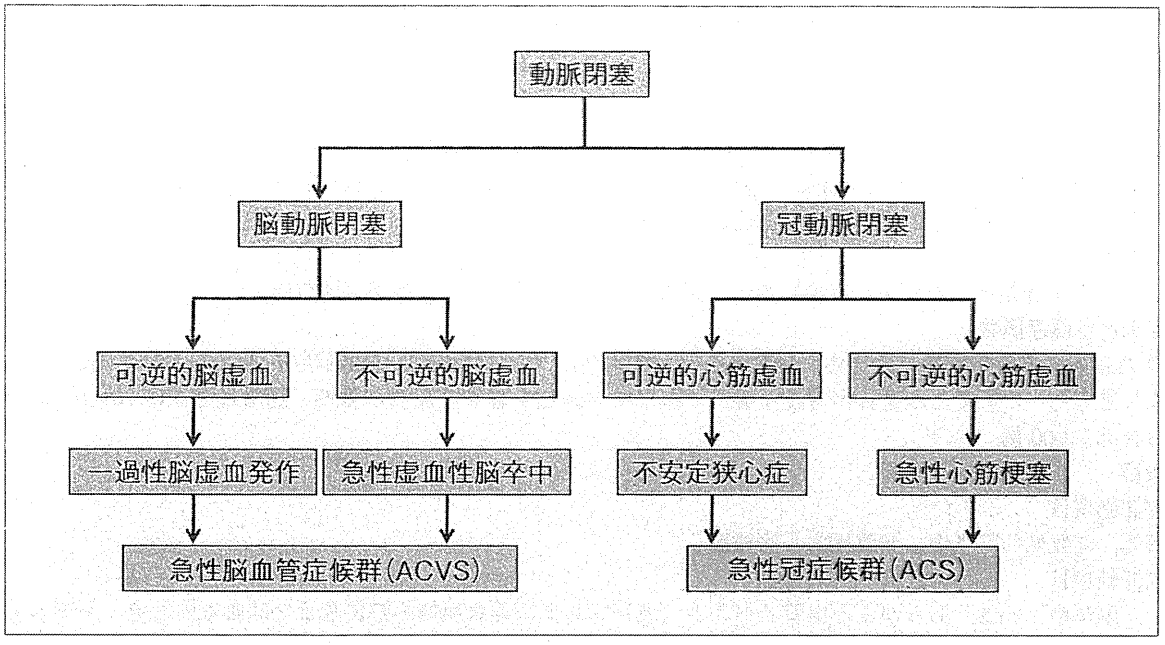

図3　急性脳血管症候群と急性冠症候群の概念図

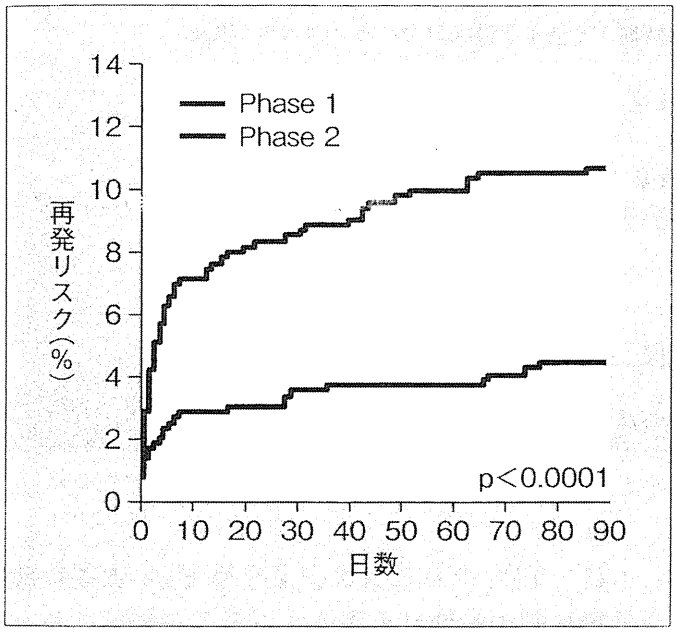

図4　TIA 発症後 90 日間の脳卒中再発リスク

Phase 1：2002 年 4 月～2004 年 10 月，プライマリーケア診療医は TIA が疑われたらファックスで専門医に相談していたが TIA に入院が必要だとは考えていなかった．

Phase 2：2004 年 10 月～2007 年 3 月，プライマリーケア診療医は患者を TIA クリニックに直接送るよう要請するようになった．

（Rothwell PM, et al.：Lancet 370：1432-1442, 2007[6] より引用改変）

制を構築して大きな成果をもたらしたことが報告されている．

以下に述べるような TIA は脳卒中発症リスクが高く，危険なので帰宅させることなく緊急入院させ，早急に治療方針を決定し，治療を開始する必要がある[8]．①ABCD^{2}スコア[9]のような脳卒中リスクスコアが高い，②MRI 拡散強調画像で虚血病巣を認める[10]，③MRA，CTA，超音波検査などで頭蓋内外の主幹動脈に 50%以上の狭窄を認める[10]，④心房細動を合併している[8]，⑤血液凝固異常症を合併している[8]，⑥2 回以上の TIA 発作（dual TIA および crescendo TIA）があった[8]．

□ TIA の国際共同観察研究

現在，TIA の大規模な国際多施設共同研究による前向き観察研究（TIAregistry. org）が進行中である．研究計画の概要を**表**に示す[11]．研究代表者はパリの Pierre Amarenco 教授であり，運営委員は筆者を含む欧州，北米，アジアの医師 13 名である．本研究は TIA クリニックをベースとした医師主導型の前向き登録観察研究である．対象は，発症後 7 日以内の TIA と AIS（modified Rankin Scale 0 または 1）であり，全世界で 5,000 例を登録し，5 年間追跡調査する予定である．

一次エンドポイントは脳卒中，心筋梗塞，心血管死であり，二次エンドポイントはこれらの心血管イベントと脳卒中・TIA，血管内治療，血行

表　TIA Registry Org. の研究計画概要

1．研究組織
研究代表者：P Amarenco（France）
運営委員：GW Albers（US），GA Donnan（Australia），J Ferro（Portugal），MG Henericci（Germany），C Johnston（US），PC Lavalee（France），J-L Mas（France），PM Rothwell（UK），PA Teal（Canada），P-J Touboul（France），S Uchiyama（Japan），E Vicant（France），KSL Wong（Hong Kong）

2．研究デザイン
TIA クリニックを基盤としたウェブ登録に基づく国際多施設共同研究による前向き観察研究．

3．対象症例と目標症例数
18 歳（または各国の法定年齢）以上の，発症後 7 日以内の TIA または軽症虚血性脳卒中（Rankin 0 または 1）で，登録前に承諾書に署名し，2 年ごとの受診が可能な症例．脳卒中の既往を有する症例は除外．登録目標数は 10ヵ国以上の 20～30 施設から合計 5,000 例．

4．評価項目
1）主要評価項目
心血管死，非致死的脳卒中，非致死的心筋梗塞
2）二次評価項目
脳卒中，脳卒中・TIA，あらゆる心血管イベント（致死的および非致死的心筋梗塞または血管内治療・血管形成術，バイパス手術，アテローム血栓性イベントによる入院），あらゆる血管内治療（血管形成術・ステント，CABG，頸動脈再建術，肢切断），追跡期間中の血圧コントロール
3）探索的評価項目
治療内容（ガイドラインと比較した脳卒中と TIA の管理），臨床症状，原因，インフルエンザワクチンの影響，社会経済（所得水準，雇用状態，医療保険の内容），発症から初診までの時間，リスク予測スコア，うつスコア（IQ8）

5．主要なデータの回収
ベースライン，1ヵ月，3ヵ月，1 年，2 年（初回の解析），3 年，4 年，5 年

6．附随研究
1）登録時，8 日時，3ヵ月時の MRI と 24 時間以内の拡散強調画像（DWI）
2）総頸動脈の内膜中膜複合体厚（IMT）と新たなプラークを検索するための登録時，3ヵ月時，5 年時の頸動脈プラーク
3）登録時または登録時と 1ヵ月時の 24 時間血圧モニター

7．背景因子
1）症状，徴候，時刻
2）CT・MRI，MRA，経胸壁心エコー，経食道心エコー，心電図，BMI，腹囲
3）主な危険因子，血管疾患の既往
4）血液検査：ヘマトクリット，血小板数，LDL・HDL コレステロール，収縮期・拡張期血圧，血糖

（内山真一郎：分子脳血管病 8：422-426，2009[11] より引用）

再建術，出血性合併症，血圧管理である．探索的エンドポイントとして治療の質（脳卒中と TIA の管理，ガイドラインとの比較），臨床症状，病因，受診のタイミング，リスク予測スコア，画像所見などを調査する．調査は登録時，1ヵ月後，3ヵ月後，1～5 年後の 8 回行われ，ウェブによる調査票の記載は臨床治験コーディネーター（CRC）が担当し，グローバルによる厳格な査察と管理が行われる．

本研究により，救急疾患としての TIA の診療実態に関する海外との比較，リスクスコアの検証，心血管イベントのリスク，危険因子や画像所見の重要性，TIA の診断基準の妥当性などに関して，多くの有益な情報が得られることが期待されるとともに，TIA クリニックのような TIA 患者の救急診療体制の整備にも寄与することが期待される．

日本からは 6 施設（東京女子医大，中村記念病院，秋田脳血管研究センター，国立循環器病研究センター，神戸医療センター，九州医療センター）が参加し，300 症例の登録を目標としている．海外でも日本でも症例登録は順調に推移し，2011 年 12 月にはいずれも目標症例数の登録を終了できるものと思われる．

□ 急性脳血管症候群の意義

急性発症の虚血性局所神経症状は TIA と AIS に共通の症状である．症状の持続時間のみから TIA と AIS を区別するのは困難であり，時間の

みで区別するのは意味がない．組織診断という観点からは，MRI 拡散強調画像（DWI）によりTIA と AIS を区別することが考えられるが，DWI を施行できない場合には鑑別できず，DWI を施行するタイミングによっても結果が左右される．また，たとえ DWI により TIA と AIS を鑑別できたとしても，病態は同一スペクトラム上にあり，治療方針は共通である．このような TIA と AIS の関係は不安定狭心症と急性心筋梗塞の関係と同じであると考えられる．

がん対策基本法に続いて，脳卒中対策基本法が国会で審議される予定である．TIA を ACVS の概念の下に救急疾患として捉え，早期診断と早期治療により AIS の発症を水際で防ぐことができれば，AIS 発症後の t-PA を含む急性期医療，リハビリテーション，介護医療など生涯にわたる莫大な医療費を節減できるため，大きな医療経済効果が期待できると考えられる．今後，TIA の救急医療体制の整備は本法の大きな柱の一つになりうると思われる．

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