ment of stroke, associations between IMT and cerebrovascular diseases are of particular interest. Chambless et al. (1996) have shown a cross-sectional association between increased IMT and stroke/transient ischemic attack (TIA). Moreover, increased IMT has been found to be a risk factor for future stroke. In the Rotterdam Study, each 1-SD change in the mean IMT increased the risk for stroke by 34% in asymptomatic volunteers over 2.7 years, independent of traditional risk factors (Bots et al. 1997a). The Cardiovascular Health Study showed that each 1-SD change in the maximum IMT was independently associated with an increase in the yearly incidence of stroke by 28% in asymptomatic volunteers (O'Leary et al. 1999). Thus, evaluation of CCA IMT may be of value for the risk assessment of stroke.

However, stroke is a heterogeneous disease that comprises several subtypes with different etiologies. Currently, studies relating IMT to stroke subtypes are limited. Touboul et al. (2000) have demonstrated greater IMT in patients with all major stroke subtypes compared with the controls, and the difference persisted after adjustments for cardiovascular histories. Because atherosclerosis is a precursor for atherothrombotic infarction, increased IMT is a reasonable risk factor for this stroke subtype. The rationale is reinforced by an association between carotid and major cerebral artery atherosclerosis (Young et al. 1960). By contrast, lacunar infarction is most often the result of lipohyalinosis, fibrinoid necrosis or microatheroma in intracerebral small arteries (Barnett et al. 1998), diluting the implication of IMT for this stroke subtype. Furthermore, atherosclerosis is not likely to play a direct role in cardioembolic infarction, intracerebral and subarachnoid hemorrhage. Large prospective studies are still necessary to establish the implication of CCA IMT for respective stroke subtypes.

Increased CCA IMT as a risk factor for peripheral artery occlusive disease. Lower extremity peripheral artery occlusive disease is another manifestation of atherosclerosis. By the time the initial symptom of intermittent claudication develops, there is already an increased propensity to cardiovascular morbidity and mortality. Reduction of ankle-to-arm pressure index is an early indicator of the disease, preceding the manifestation of claudication. Given the association between the carotid and femoral artery atherosclerosis (Wendelhag et al. 1993), increased CCA IMT is linked both to a reduction of the index (Allan et al. 1997) and to intermittent claudication (Allan et al. 1997). Based on these findings, increased IMT may serve as a marker for the existence of peripheral artery occlusive disease. Of note, the Rotterdam Study has shown that each 0.1-mm increase in the mean IMT is associated with an age- and gender-adjusted reduction of the ankle-to-arm pressure index of 0.026 (Bots et al. 1994). This result may be of aid for the identification of patients during presymptomatic stages, suggesting an additional benefit of IMT measurements for cardiovascular risk assessment. However, whether earlier diagnosis and aggressive risk factor modification improve the outcome remains to be determined.

Plaques

Plaque existence and quantity. If atherosclerosis begins with minor changes in IMT, atheroma formation and the subsequent encroachment into the lumen represent later stages (Zureik et al. 2000). Thus, existence of carotid artery atheromas, observed as plaques by US, might imply even higher cardiovascular risk than a diffuse increase in IMT. Ebrahim et al. (1999) have shown that existence of such plaque is more strongly associated with cardiovascular risk than IMT measurements. Also, carotid plaques have been associated with left ventricular hypertrophy (Roman et al. 1995), impaired cognitive function (Breteler et al. 1994), cerebral white matter lesions (Bots et al. 1993a) and a history of stroke/TIA (Iannuzzi et al. 1995), whereas the plaque enlargement increased the risk for ipsilateral neurological events (Weinberger et al. 1988). Moreover, existence of such plaques was an indicator of coronary stenosis that is equivalent to an ischemic exercise ECG in a population with a high prevalence of CAD (Nowak et al. 1998). On the basis of these findings, identification of carotid plaques may be an aid in the risk assessment of cardiovascular diseases.

In addition to their existence, the quantity of plaques reflects cardiovascular risk in an individual. For the quantification of carotid plaques, Crouse et al. (1986) suggested a scoring system, showing its associations with cardiovascular risk factors and CAD (Crouse et al. 1987). Later, the scoring system was modified by Handa et al. (1990), and was termed the "plaque score" (PS). PS is defined as the sum of all plaque heights in bilateral extracranial carotid arteries. Because PS increases in parallel with the height and number of atheromas, it may allow for the quantification of relatively advanced carotid atherosclerosis. PS is associated with atherosclerotic risk factors (Hashimoto et al. 2001; Mannami et al. 1997), and is higher in subjects with CAD (Tanaka et al. 1992) or cerebral infarction (Hougaku et al. 1994; Nagai et al. 2001b). Also, PS was a predictor for future stroke in a population at higher cardiovascular risk (Handa et al. 1995). These findings suggest the potential utility of carotid plaque quantification for cardiovascular risk assessment. However, partly due to the lack of large prospective studies, the benefits of such scoring systems over IMT measurements are not known.

Plaque echogenicity. Disruption of carotid artery plaques is thought to be a cause of cerebral embolism. The susceptibility for disruption is related to the plaque fragility determined by its content. Higher proportion of lipid and intraplaque hemorrhage increases the fragility, which may predispose to intimal tears, initiating the clotting cascade with subsequent thrombus formation on the surface. Thus, detection of lipid and hematoma components may help identify unstable plaques with a greater risk for embolization.

Studies have related plaque echogenicity to the histological content. It is generally known that fibrous plaques and calcification are relatively hyperechoic, and lipid and thrombus components are hypoechoic. Heterogeneity in the plaque echogenicity is associated with intraplaque hemorrhage (Bluth et al. 1986). However, because B-mode imaging does not distinguish between lipid and hematoma (Beletsky et al. 1996), the accuracy to diagnose intraplaque hemorrhage is only moderate. Also, larger plaques often have complex structures, precluding reliable US images. Nevertheless, the existence of hypoechoic and heterogeneous plaques increases the risk of future neurological events (Iannuzzi et al. 1995; Mathiesen et al. 2001; Polak et al. 1998), suggesting potential utility in evaluating plaque echogenicity for stroke risk assessment.

Spectrum analysis of backscatter echo signals, a useful technique for myocardial tissue characterization (Di Bello et al. 1995), may be of aid for the discrimination between lipid and hematoma in carotid plaques (Noritomi et al. 1997). The use of this technique could refine the interpretation of plaque-related risk for stroke. Currently, this technique is costly and available only in limited clinical laboratories.

Plaque ulceration. In addition to plaque echogenicity, the surface appearances are related with the risk of stroke. Particularly, ulceration of carotid plaques represents an embolic source to the cerebral arteries (Sitzer et al. 1995). With the use of US, studies have linked carotid plaque ulcers to the risk of future stroke (AbuRahma et al. 1998; Handa et al. 1995). Also, increased platelet accumulation has been demonstrated at such ulcers, suggesting their thrombogenic nature (Moriwaki et al. 1995). On the basis of these findings, US identification of carotid ulcers may be of value for the risk assessment of stroke. Nonetheless, the diagnostic accuracy of US is controversial, limiting the data on their *in vivo* properties. Given the controversies regarding US diagnosis of ulcers, an international consensus report has recommended diagnosing only large obvious excavations as ulcers (de Bray et al. 1997). The utility of such strict criteria still needs to be validated.

Carotid stenosis. Compared to the common carotid artery, carotid bifurcation and internal carotid artery (ICA) are more prone to plaque formation, often causing stenosis. B-mode imaging enables visualization of the lesion of stenosis, allowing for direct measurements of original and residual lumen. However, stenotic lesions are often hypoechoic as is blood echogenicity, or contain calcification that interferes with US. Also, loss of US occurs in larger plaques, often making it difficult to identify the plaque-blood interface. Because of such technical problems, accuracy of B-mode is not high for the quantification of carotid stenosis (Ricotta et al. 1987). Alternatively, severity of carotid stenosis can be diagnosed based on blood flow velocity at the site of stenosis. A review of the literature suggests a high accuracy of such diagnoses (de Bray and Glatt 1995), and the current criteria for grading stenosis are primarily based on the Doppler and/or duplex findings (Zwiebel 1997).

Asymptomatic carotid stenosis (Sterpetti et al. 1988) and its progression (Muluk et al. 1999) increase the risk of future stroke. Also, such asymptomatic stenosis is associated with higher mortality in the general population (Joakimsen et al. 2000). Currently, there are some therapeutic strategies for such stenosis. For example, carotid endarterectomy is beneficial even for asymptomatic patients when the stenosis is $\geq$ 60% and the local surgical risk is low (Gorelick et al. 1999). Moreover, progression of stenosis is mitigated by the treatment of hypertension (Sutton-Tyrrell et al. 1994). Thus, earlier diagnosis by US could potentially lead to risk reduction for cardiovascular morbidity and mortality. Nonetheless, clinical data are still limited, requiring further studies to determine the optimal treatment for such individuals.

HEMODYNAMICS

Numerous articles exist regarding the Doppler criteria for diagnosing carotid stenosis/occlusion. In addition, because the Doppler waveforms are affected by pathophysiological properties of the arterial system, they could convey useful information for cardiovascular risk assessment. Among many indices proposed to characterize the Doppler waveforms, commonly known are pulsatility index and resistive index (Evans et al. 1989). Additionally, we have introduced "decay index" to reproduce the postpeak portion of carotid Doppler waveforms (Nagai et al. 1999c, 2001a). Nonetheless, because all such indices are affected by many factors, including peripheral resistance, valvular function and heart rate, their diagnostic utilities may be limited.

Nevertheless, reduction of carotid pulsatility index was associated with postmenopausal estrogen replacement therapy (Jackson and Vyas 1998), a cardiovascular

protector in women. Inversely, increased pulsatility index was associated with diabetic microvascular complications (Lee et al. 2000). Moreover, carotid resistive index was as strongly associated with cardiovascular risk as CCA IMT (Frauchiger et al. 2001). These findings suggest the potential utility of such indices as a reflector of arterial health. Further studies are necessary to determine their value for cardiovascular risk assessment.

ELASTICITY

Assessment of carotid artery elasticity

With the use of US, elastic properties of the CCA are commonly evaluated from the diameter changes for a given distending pressure. At current, although the echo-tracking method (Reneman et al. 1986) is most accurate for measuring the diameter, the equipment is costly and, thus, available only in research centers. Alternatively, CCA elastic properties can be assessed with the use of standard B-mode (Barth et al. 1988; Nagai et al. 1999b) and M-mode (Gamble et al. 1994) US. Although neither method is as accurate as echo-tracking for measuring the diameter changes, they are readily available in the clinic. For the evaluation of distending pressure, blood pressure (BP) should ideally be assessed where the diameters are measured, but is often derived from the brachial artery in practice. However, because of the pressure wave reflection, brachial BP is different from carotid BP, provoking controversies regarding the use of such nonsimultaneous BP measures for the CCA elasticity evaluation.

Several indices are used to evaluate elastic properties of the CCA, including "distensibility coefficient (DC), compliance (CC)" and "Peterson's pressure-strain elastic modulus (Ep)":

$$DC = (2\Delta d/D) / \Delta p \quad (1)$$

$$CC = \pi D\Delta d / 2\Delta p \quad (2)$$

$$Ep = \Delta p / (\Delta d/D) \quad (3)$$

where Δp is pulse pressure, Δd is the difference between systolic and diastolic diameter, and D is either end-diastolic or average diameter. Reneman et al. (1996) claim it should be the average diameter, although there is no consensus. For more details, refer to the literature (Reneman and Hoeks 2000), in which concepts of respective measures are clearly defined.

Although arterial stiffness is closely associated with BP, the association with hypertension has been controversial. Because BP is involved in the definition of the moduli, statistical concerns exist when analyzing BP effect on arterial elasticity. Several approaches have been used to separate BP effect from elasticity. One method is a mathematical correction for the BP effect (Liu et al. 1989). However, the interpretation requires additional mathematical knowledge, precluding common usage in the clinic. A different approach is the use of the "stiffness index (β)" (Hirai et al. 1989):

$$\beta = \ln (\text{systolic BP/diastolic BP}) / (\Delta d/D) \quad (4)$$

By introducing the logarithm of the ratio of systolic to diastolic BP, this index is relatively independent of transient changes in BP (Hirai et al. 1989). Because of the convenience, the stiffness index is increasingly used in clinical studies.

Carotid arterial stiffness as a potential cardiovascular risk factor

Increased arterial stiffness, as defined by the loss of elasticity, is thought to represent a risk factor for cardiovascular diseases (Cameron 1996). Although CCA stiffness is often evaluated in relation to cardiovascular risk factors, the CCA is much less prone to atherosclerosis than the carotid bifurcation and ICA (Li et al. 1994), raising a question about the rationale for its evaluation. By contrast, increased stiffness of the aorta mechanically leads to systolic BP elevation and left ventricular hypertrophy (Nichols et al. 1985), and has been associated with the risk of future cardiovascular events (Boutouyrie et al. 2002; Laurent et al. 2001). Given such conditions, we have shown an association between CCA and aortic stiffness, independent of traditional cardiovascular risk factors (Nagai et al. 1999b). The finding suggests the potential utility of CCA stiffness as a surrogate for the systemic arteries, supporting the rationale for evaluating CCA stiffness in cardiovascular risk assessment.

CCA stiffness increases with age (Reneman et al. 1986) and in the presence of hypertension (Arcaro et al. 1991), hyperlipidemia (Riley et al. 1986), diabetes (Salomaa et al. 1995) and smoking (Failla et al. 1997). We have shown reduced CCA stiffness in postmenopausal women on estrogen replacement therapy (Nagai et al. 1999a). Moreover, CCA stiffness has been associated with atherosclerosis at various sites in the vascular tree (van Popele et al. 2001) and was a predictor of cardiovascular mortality in end-stage renal disease (Blacher et al. 1998). However, prospective studies are still limited, requiring further studies to determine whether or not the CCA stiffness provides clinically useful information for cardiovascular risk assessment.

CLINICAL APPLICATION

Technical problems

Based on studies to date, evaluation of carotid arterial properties appears to be of value for cardiovascular

risk assessment in apparently healthy individuals. However, there are some technical problems for its clinical applications. First, the majority of findings were derived from research laboratories, where measurement protocols were tightly controlled, in the absence of established standards. For instance, consensus is lacking regarding whether the mean or maximum IMT should be used, with no agreement on the normative ranges or, alternatively, certain cutoffs. Second, accuracy of clinical US equipment is not necessarily sufficient, particularly when evaluating arterial elastic properties. Notably, CCA diameter changes as assessed by B- or M-mode methods could be even inaccurate when arterial walls move only a little. Under such conditions, if the findings derived from research environments replicate in the clinic is not guaranteed. Recently, Baldassarre et al. (2000) have shown that both the mean and maximum IMT measured by the standard B-mode have a similar reproducibility and associations with cardiovascular diseases to those reported from research laboratories. Also, Stadler et al. (1997) have shown that the B-mode method has a similar reproducibility to that of echo tracking for assessing CCA diameters on different occasions, although controversies exist. Given these findings, standardization of the measurement protocols and definition of the normative ranges should precede the clinical application of additive carotid evaluations.

Cost-labor benefit relationships

In addition to such technical problems, practical utilities of carotid evaluations may need to be determined with regard to cost-labor benefit relationships. First, under the cost containments of health care systems in North America, screening for asymptomatic individuals is not generally justified (del Sol et al. 2001), limiting the examination only for symptomatic patients or those with asymptomatic carotid bruits. Second, when carotid arterial properties are to be evaluated during the routine check for stenosis, additional time and effort is necessary. Particularly, evaluation of elastic properties is time-consuming and requires skilled sonographers, which may be beyond the possibility of current clinical practice. Third, diagnostic utilities of carotid properties, except for stenosis, are generally low. For instance, because IMT overlaps between patients with cardiovascular disorders and those without, increased IMT is more likely a risk factor than a diagnostic marker. These issues are still to be addressed when applying additive carotid measurements in the clinic, requiring further work to determine whether such measurements are of value for clinical purposes.

SUMMARY

Carotid arterial properties appear to be associated with cardiovascular risk in apparently healthy individuals, providing a noninvasive window for watching the risk. Because most of such properties can be evaluated in the clinical setting of carotid ultrasonography, the evaluation could potentially extend the benefits of examination. However, in addition to the technical problems for clinical applications, the practical value of evaluations remains to be determined with regard to cost-labor benefit relationships of examining asymptomatic individuals at risk.

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● *Original Contribution*

CAROTID ARTERY INTIMA-MEDIA THICKNESS AND PLAQUE SCORE FOR THE RISK ASSESSMENT OF STROKE SUBTYPES

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Abstract—As measures for the severity of carotid atherosclerosis, we compared common carotid artery (CCA) intima-media thickness (IMT) and plaque score (PS) for risk assessment of respective stroke subtypes. The subjects comprised 792 nonstroke and 311 stroke patients, including 72 with atherothrombotic infarction (AI), 113 with lacunar infarction (LI), 54 with cardioembolic infarction and 29 with cerebral hemorrhage. IMT was bilaterally measured on CCA far walls, and averaged. PS was obtained by summing up the maximum thickness of all plaques in bilateral carotid arteries. Both IMT and PS were greater in AI and LI patients than in nonstroke patients (all $p < 0.05$), but similar between other subtype and nonstroke patients. By receiver operating characteristic (ROC) curve analyses, both measures discriminated the likelihood for AI and LI (all $p < 0.05$), but not for other subtypes. When discriminating AI, ROC area defined by PS (0.80) was greater than that defined by IMT (0.68) ($p < 0.05$). Thus, although both CCA IMT and PS appear to help for risk assessment of AI and LI, risk of AI may be more effectively assessed by PS. (E-mail: nagaiy@medone.med.osaka-u.ac.jp) © 2002 **World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Carotid arteries, Stroke, Atherosclerosis, Ultrasound, Risk factors.**

INTRODUCTION

Ultrasound (US) has allowed for a noninvasive observation of atherosclerosis in the carotid arteries, including wall thickening, atheromatous plaques and stenosis. Common carotid artery (CCA) wall thickness is often evaluated by measuring its intima-media thickness (IMT), representing an indicator for early carotid atherosclerosis. Based on studies to date, increased CCA IMT has been associated with the risk of stroke (Bots et al. 1997a; O'Leary et al. 1999). However, CCA is less prone to atherosclerosis than the carotid bifurcation, and if a slight increase in IMT represents local atherosclerosis is controversial (Bots et al. 1997b; O'Leary et al. 1996). Given such controversies, formation of localized plaques and subsequent protrusion into the lumen represent later stages of atherosclerosis (Zureik et al. 2000). Ebrahim et al. (1999) have shown that existence of carotid plaques is more strongly associated with cardiovascular risk than a diffuse increase in IMT. For the quantification of such plaques, we have used the plaque score (PS) and shown its associations with stroke risk (Handa et al. 1990, 1995). Taken together, both CCA IMT and PS appear to be of aid for the risk assessment of stroke.

However, stroke is a heterogeneous disease that comprises several subtypes with different etiologies. Because atherosclerosis is a precursor for atherothrombotic infarction, carotid atherosclerosis is a reasonable risk factor for this stroke subtype. Lacunar infarction is most often the result of lipohyalinosis, fibrinoid necrosis or microatheroma in intracerebral small arteries (Barnett et al. 1998), diluting the implication of carotid atherosclerosis. Moreover, atherosclerosis is not likely to play a direct role in cardioembolic infarction, intracerebral and subarachnoid hemorrhage. Nevertheless, studies relating carotid atherosclerosis and stroke subtypes have been limited. Touboul et al. (2000) have demonstrated similarly greater CCA IMT in all major cerebral infarction subtype patients, compared with the controls. By contrast, we have shown greater PS only in atherothrombotic and lacunar infarction patients than in nonstroke patients (Nagai et al. 2001). Consequently, implication of carotid atherosclerosis remains to be established for each stroke subtype.

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Table 1. Baseline characteristics

n	1103
Age (years)	62 ± 12
Gender (% men)	58
Hypertension (%)	61
Hyperlipidemia (%)	47
Diabetes mellitus (%)	23
Smoker (%)	49
CCA IMT (mm)	0.82 ± 0.21
Plaque score	5.6 ± 6.3

CCA IMT = common carotid artery intima-media thickness.

As measures for the severity of carotid atherosclerosis, this study compared CCA IMT and PS for the risk assessment of respective stroke subtypes.

MATERIALS AND METHODS

Subjects

The subjects for this investigation were enrolled from patients of the Department of Internal Medicine and Therapeutics at Osaka University Hospital, who had undergone carotid ultrasonography between January 1996 and April 2001. Many of them had histories of stroke and/or cardiovascular risk factors, such as hypertension, hyperlipidemia and diabetes. Also, they included patients with nonspecific neurological complaints, such as dizziness, headache and memory disturbances. The majority of patients had been referred from other hospitals or departments for the assessment of cerebral circulation, for the secondary prevention of stroke or for perioperative risk assessment before surgery. Because of the high prevalence of stroke and its risk factors, carotid ultrasonography was performed for the screening of carotid atherosclerosis and stenosis or, in some cases, for the assessment of vertebral artery circulation.

To mitigate direct threats to the cerebral circulation and to focus on atherosclerosis *per se*, patients with the following criteria were excluded: 1. carotid stenosis ≥ 60% or occlusion by duplex ultrasound, 2. post carotid endarterectomy, and 3. collagen diseases including Takayasu's arteritis and systemic lupus erythematosus. Also, 4. patients with transient ischemic attack (TIA) were excluded because TIA is highly heterogeneous, often very close to stroke, but not stroke.

During the study period, 1197 patients had undergone carotid examination, among whom 94 patients met one of the above criteria and were excluded. As a consequence, the subjects for this investigation comprised 1103 patients (age: 62 ± 12 years old), including 311 patients who had experienced stroke. Baseline characteristics of these patients are shown in Table 1.

The protocols of this study were approved by the Osaka University Institutional Review Board, and informed consent was obtained from all subjects after the nature of the procedures had been explained. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Carotid ultrasonography

Duplex carotid ultrasonography was performed as previously described (Handa et al. 1990), with the use of linear-array 7.5-MHz transducers (EUB-525, Hitachi, Inc., Tokyo, Japan; SSA-260A, Toshiba, Inc., Tokyo, Japan). Briefly, the subject lay in the supine position in a dark room, and the examinations were done with the head held in the midline position or slightly tilted to either side.

For evaluation of CCA IMT, the transducer was manipulated so that the near and far walls were parallel to the transducer footprint and the lumen diameter maximized in the longitudinal plane. A region approximately 1.5 cm proximal to the flow divider was identified, and far-wall IMT was evaluated as the distance between the luminal-intimal interface and the medial-adventitial interface. IMT was measured on the frozen frame of a suitable longitudinal image with the image magnified to achieve a higher resolution of detail. The measurement was obtained from four contiguous sites by approximately 5-mm intervals, and the overall mean of both sides was used for analyses.

Calculation of PS was done in accordance with our prior studies (Handa et al. 1990; Hashimoto et al. 2001; Nagai et al. 2001). Briefly, the common and internal carotid arteries were scanned cross-sectionally and longitudinally, whereby distribution of atheromatous plaques (localized increases in IMT ≥ 1.1 mm) was roughly evaluated. During the initial scanning, optimal insonation angles were determined to measure the maximum thickness of plaques, and the measurement was performed on the frozen frame, perpendicular to the vascular walls (Fig. 1). Bilateral carotid arteries were examined following the same procedures. Thereafter, PS was computed by summing up the thickness of all plaques located in bilateral carotid arteries, where PS was calculated to be a dimensionless number. Length of individual plaques was not considered for the calculation of this score.

Carotid stenosis/occlusion was diagnosed by the commonly used criteria (Bluth et al. 1988).

All measurements were performed by the strokologists (stroke neurologists/cardiologists) of our department, who were skilled in carotid US examinations (Y. Nagai, H. Yamagami, K. Kondo, H. Hougaku). When interobserver reproducibility was assessed for 14 patients, the interrater correlation of IMT was 0.82 and 0.76 for PS, with similar averages between the arbitrary pairs

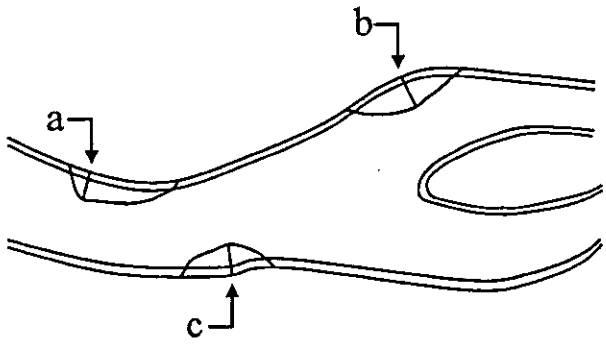

Fig. 1. Calculation of the plaque score. PS is computed by summing up the maximum thickness (in mm) of each plaque located in bilateral carotid arteries, where it is calculated to be a dimensionless number (*i.e.*, PS = a + b + c + contralateral plaques).

of examiners (IMT: 0.80 ± 0.17 vs. 0.84 ± 0.20, PS: 10.2 ± 8.5 vs. 11.2 ± 8.2).

Diagnoses of stroke and its subtypes

Neurological signs and symptoms were evaluated by the strokologists of our department, when patients visited and/or were admitted to the hospital. Histories of neurological episodes were carefully obtained from the patients and/or their families. On the basis of neurological signs/symptoms and medical histories, stroke was diagnosed by an acute disturbance of focal neurological function resulting in either signs or symptoms of presumed vascular origin that persisted for > 24 h. Patients diagnosed to have stroke subsequently underwent brain MRI scans, which were used as diagnostic aids for stroke subtypes.

On the basis of neurological signs/symptoms, medical histories and brain scans, patients were classified into the following six groups, in accordance with our prior study (Nagai et al. 2001): nonstroke, atherothrombotic infarction (AI), lacunar infarction (LI), cardioembolic infarction (CE), cerebral hemorrhage (CH) and other or unclassified stroke (OU).

Conceptually, AI is the stroke due to carotid and major cerebral artery occlusion, in the absence of cardiac embolic sources. LI is the stroke with consciousness and higher cerebral function maintained in the setting of one of the typical lacunar syndromes, with a small deep infarction in the territories supplied by perforating branches of major cerebral arteries. CE is the stroke caused by cardiac embolic sources, including left atrial thrombus, persistent or paroxysmal atrial fibrillation/flutter and myocardial infarction. CH comprises cerebral, cerebellar or brain-stem hemorrhage, as evidenced by hematoma or its scar.

Because all evaluations were done as parts of the routine clinical work, the strokologists involved in diagnoses were not completely blind to the carotid findings. Thus, to reinforce the diagnostic objectivity, the subtypes were always diagnosed by more than one strokologist, with the final diagnoses made by consensus.

Data analyses

CCA IMT and PS were compared between nonstroke and respective stroke subtype patients, by independent *t*-test and, thereafter, by adjusting age and gender. Subsequently, ability of these measures to discriminate the likelihood of specific stroke subtypes was examined by receiver-operating characteristic (ROC) curve analyses. ROC curve is a graph that displays the relationship between sensitivity and specificity of a diagnostic tool across a spectrum of cutpoints that could be used to classify patients as diseased or nondiseased. Overall accuracy of the diagnosis is expressed in terms of the area under the ROC curve, ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination). Generally, a value of > 0.7 can be interpreted as reasonable, and a value > 0.8 can be interpreted as good. Differences in discriminative value between CCA IMT and PS were examined based on ROC area defined by these measures.

Data are presented as mean ± SD unless otherwise specified, and a two-tailed p value < 0.05 was considered to be statistically significant. All analyses were performed with the use of SPSS 9.0 (SPSS Japan Inc., Tokyo, Japan).

RESULTS

CCA IMT and PS in nonstroke and respective stroke subtype patients

Stroke was diagnosed in 311 of 1103 patients, including 72 AI (23% of total stroke), 113 LI (36%), 54 CE (17%), 29 CH (9%) and 43 OU (14%) (Table 2). As measures for the severity of carotid atherosclerosis, both mean CCA IMT and PS were greater in AI and LI than in nonstroke patients, whereas significant differences were not found between other stroke subtype and nonstroke patients. Additionally, adjustments of age and gender little modified the magnitudes of both measures, and the differences found for AI and LI persisted.

CCA IMT and PS for the risk assessment of specific stroke subtypes

To further compare CCA IMT and PS to discriminate the likelihood for specific stroke subtypes, we performed ROC curve analyses (Table 3). Both when using IMT and PS, the ROC areas found for AI and LI were greater than 0.5, which was not the case for other stroke subtypes. Of note, when discriminating AI, the ROC area

Table 2. CCA IMT and plaque score in nonstroke and respective stroke subtype patients

	Nonstroke	AI	LI	CE	CH	OU
n	792	72	113	54	29	43
CCA IMT (mm)	0.81 ± 0.21	0.92 ± 0.18*	0.91 ± 0.21*	0.79 ± 0.17	0.77 ± 0.16	0.83 ± 0.25
Plaque score	4.9 ± 5.9	11.7 ± 7.0*	7.9 ± 6.7*	4.4 ± 5.4	5.0 ± 5.0	4.5 ± 6.7
Age (years)	61 ± 12	64 ± 9	64 ± 10	62 ± 13	60 ± 8	59 ± 15
Gender (% men)	54	82	66	67	72	58

AI = atherothrombotic infarction; LI = lacunar infarction; CE = cardioembolic infarction; CH = cerebral hemorrhage; OU = other or unclassified stroke; CCA IMT = common carotid artery intima-media thickness, * $p < 0.05$ compared to nonstroke patients.

defined by PS was greater than that defined by IMT (Fig. 2).

DISCUSSION

Because the study sample comprised patients of our department, prevalence of stroke was high, with 1 of 4 patients diagnosed as having strokes. Proportions of respective stroke subtypes were in agreement with other studies derived from our country (Fujishima 1996). Compared with nonstroke patients, both CCA IMT and PS were greater in AI and LI patients (Table 2), suggesting increased severity of atherosclerosis in such patients. However, magnitudes of these measures were similar between other stroke subtype and nonstroke patients. The finding is consistent with the fact that atherosclerosis does not always play a direct role in CE, CH and OU. The greater CCA IMT found for AI and LI patients is in agreement with Touboul et al. (2000). Nonetheless, they have demonstrated greater IMT also in CE patients, which was not the case in the current study. Because evaluation methods for IMT were similar between this study and theirs, such a difference could have been caused by characteristics of the study samples. Namely, they obtained the controls primarily from noncardiovascular patients with lower IMT, whereas our nonstroke patients predominantly comprised cardiovascular patients with higher IMT. Additionally, as a part of diagnostic criteria for CE in both studies, myocardial infarction is associated with carotid atherosclerosis, whose prevalence could affect average IMT in CE patients.

To further compare CCA IMT and PS for the risk assessment of respective stroke subtypes, we performed ROC curve analysis. The analysis is a statistical procedure that compares the utilities of diagnostic tools based on their sensitivity and specificity. With the use of this analysis, both CCA IMT and PS significantly discriminated AI and LI from nonstroke patients (Table 3), suggesting potential benefits of carotid evaluation for the risk assessment of such stroke subtypes. However, neither of these measures discriminated CE, CH and OU from nonstroke patients, limiting the significance of carotid evaluation for such stroke subtypes. Of note, when discriminating the likelihood for AI, the ROC area defined by PS was greater than that defined by IMT (Fig. 2). Based on this result, evaluation of PS appears to be more effective than CCA IMT measurements for the risk assessment of AI. The finding was not unexpected, because PS is directly derived from atheromatous plaques that represent a precursor for AI. However, when carotid atherosclerosis is extensive, evaluation of PS could require additional efforts, precluding determination of whether or not PS is clinically superior to IMT as a risk indicator for AI.

The current study has limitations similar to our prior study (Nagai et al. 2001), in the diagnosis of stroke subtypes and transferability to the general population. Additionally, because this study is cross-sectionally designed, if the findings can be applied to presymptomatic individuals is not clear. Finally, consensus is lacking regarding the standard of IMT measurements (*e.g.*, mean vs. maximum, inclusion of focal plaques or not). Nonetheless, mean CCA IMT is often evaluated as an indicator for carotid atherosclerosis (Bonithon-Kopp et al. 1996; Bots et al. 1997a; Ferrara et al. 1994; Nagai et al. 1999; Touboul et al. 2000), supporting the potential value of our findings.

Table 3. ROC curve analyses for discriminating the likelihood of respective stroke subtypes

	AI	LI	CE	CH	OU
CCA IMT	0.68 (0.62–0.74)*	0.64 (0.59–0.69)*	0.51 (0.43–0.58)	0.53 (0.43–0.63)	0.51 (0.41–0.61)
Plaque score	0.80 (0.76–0.84)*†	0.67 (0.62–0.71)*	0.53 (0.45–0.61)	0.54 (0.45–0.64)	0.55 (0.46–0.63)

See footnotes of Table 2 for abbreviations. Numbers represent the area under ROC curves, with 95% confidence intervals in parentheses; *ROC area is greater than 0.5 at $p < 0.05$, † $p < 0.05$ vs. CCA IMT.

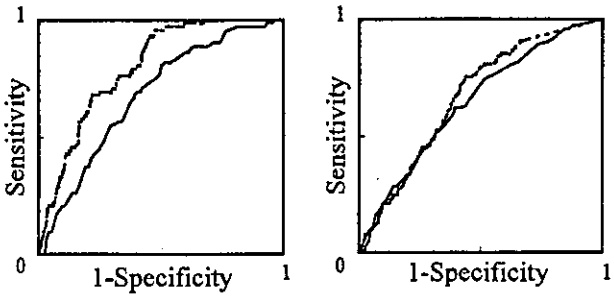

Fig. 2. Utilities of common carotid artery intima-media thickness (CCA IMT) and plaque score for discriminating the likelihood for atherothrombotic and lacunar infarction. Curves represent ROC curves, defined by CCA IMT (—) and plaque score (- - - -), for discriminating atherothrombotic (left panel) and lacunar (right panel) infarction. For atherothrombotic infarction, the ROC area defined by the PS is greater than that defined by CCA IMT ($p < 0.05$).

SUMMARY

In summary, this study demonstrated the potential value of CCA IMT and PS for the risk assessment of AI and LI, but not for other stroke subtypes. Particularly, the risk of AI may be more effectively assessed when evaluating PS. Large prospective studies are still necessary to establish the link between these measures and the future risk of specific stroke subtypes.

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虚血脳における神経前駆細胞の動態

北川一夫　松本昌泰

◎神経幹細胞の研究の進歩に伴い，各種病態下においてこれらの動態が修飾されることが明らかになってきている．脳虚血はヒト脳がもっとも遭遇する頻度の高い疾患である脳卒中，なかでも脳梗塞の根幹をなす病態であり，虚血病態における神経幹細胞の動態を明らかにすることは脳梗塞患者において，神経機能の回復を目指す再生医療的な立場から重要な課題と考えられる．著者らの研究を含め今日までの研究で，脳虚血侵襲に際して海馬や側脳室下層に存在する神経幹細胞または神経前駆細胞の分裂・増殖が促進され，とくに海馬では増殖細胞は成熟神経細胞に分化することが明らかになってきている．しかし，虚血侵襲に際して神経幹細胞の分裂・増殖を規定している要因は明らかでなく，またいったん分裂・増殖した神経細胞の生存維持や分化を規定する因子も明らかではない．臨床現場で後遺症に苦しむ多くの脳卒中患者に，神経幹細胞の増殖，神経細胞新生を促進して神経細胞再生という夢を実現するには，克服されるべき多くの基礎的検討課題が残されている．

Key word：神経幹細胞，neurogenesis，Musashi 1，虚血

成熟動物脳でも神経幹細胞または神経前駆細胞が特定の限られた領域，側脳室下層(subventricular zone：SVZ)と海馬歯状回顆粒下層(subgranular zone：SGZ)に存在し，それぞれ嗅球，海馬歯状回での神経細胞新生に寄与していることが明らかになってきた．これらの領域に存在する神経幹細胞は，脳由来神経栄養因子(brain-derived neurotrophic factor：BDNF)をはじめとした各種の神経栄養因子の投与で分裂・増殖が促進されるほか，生理的な環境要因，てんかん，脳虚血といった病態時においても，その動態が修飾されることが明らかになってきている．

本稿では主として脳虚血病態で検討が進んでいる海馬での神経前駆細胞動態，神経細胞新生(neurogenesis)について，著者らのデータを交えつつ解説するとともに，SVZをはじめほかの領域での神経幹細胞動態，神経細胞新生に関する現段階での知見についてまとめる．

Neurogenesis in the ischemic adult brain
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虚血海馬での神経幹細胞動態

1. 脳虚血モデルでの海馬歯状回での神経細胞新生

脳虚血モデルで最初に神経細胞新生の亢進について報告したのは，Sharpらのグループである[1]．スナネズミの両側総頸動脈5分間閉塞再灌流モデルでは海馬CA1，CA4に神経細胞死を生じるが，同モデルで虚血10日後をピークとした海馬歯状回SGZ領域での核酸チミジンのアナログであるbromodeoxyuridine(BrdU)を取り込んだ増殖細胞数の増加とその後の神経細胞への分化を示した．その後同様な一過性前脳虚血モデルを用いて，ラット[2]，マウス[3]の海馬SGZでもBrdU陽性の増殖細胞数の増加が報告された．しかし，BrdUは神経幹細胞のみならず，脳内に存在する増殖能をもった細胞，グリア細胞，ミクログリア，血管内皮細胞にも取り込まれうることを念頭においておく必要がある．とくに虚血侵襲を受けた後では，脳内で活性化されたミクログリア，マクロファージは活発な増殖能を示し，BrdUでラベルされる細胞の大部分はこれら細胞である可能性がある．このような点を考慮し，著者らが神経幹細胞の選択的マーカーであるMusashi1(Msi-1)に対する抗体を用いて虚血脳海馬での神経幹細胞の動態につい

て検討した結果を紹介する(後述)．一方，ヒトの脳梗塞に近いモデルとしてはラットやマウスの中大脳動脈閉塞モデルが存在するが，同モデルでは本来，後大脳動脈の灌流領域である海馬は虚血に曝されず，虚血遠隔領域と考えられる．しかし著者らの報告も含め，ラット[4-6]，マウス[7]ともに中大脳動脈閉塞7日後をピークとした同側のみならず，反対側海馬でのBrdU陽性の増殖細胞数の増加を認めている．

2. 虚血海馬での神経前駆細胞動態

海馬SGZに存在する神経幹細胞，または神経前駆細胞の性状について十分に解明されていないが，最近Alverez-Buyllaらのグループが，同領域のアストロサイト(星状グリア細胞)が神経前駆細胞であるとの報告を行っている[8]．神経幹細胞の選択的マーカーであるMsi-1やネスチンはアストロサイトにも存在するため，著者らは神経幹細胞マーカーが陽性で，アストロサイトのマーカーであるグリア線維性酸性蛋白質(GFAP)が陰性である細胞を神経前駆細胞とした．正常海馬では海馬SGZでBrdU陽性細胞が散見されたが，その大部分はMsi-1陽性でかつGFAP陰性であり，同領域でBrdUでラベルされる細胞の大部分は神経前駆細胞であると考えられた．ラットの4血管閉塞再灌流モデルでは虚血7日後をピークとした海馬SGZでのBrdU陽性細胞数の増加が観察されたが(図1)[9]，虚血海馬での分子マーカーを用いた検討でも正常脳と同様にSGZでのBrdU陽性の増殖細胞の大部分はMsi-1陽性，GFAP陰性であった(図1)．また，アストロサイトではMsi-1とGFAPはともに発現し，とくに海馬CA1領域では神経細胞死の発生後，反応性アストロサイトの増生が観察されるが，同領域ではMsi1-1とGFAPがともに強く発現しているのに対して，海馬歯状回SGZではMsi-1陽性細胞の多くがGFAP陰性であり，同領域のBrdU陽性，Msi-1陽性，GFAP陰性細胞が神経前駆細胞であることを強く示唆している．虚血侵襲後に分裂・増殖が促進される神経前駆細胞が，Alvarez-Buyllaらが提唱するようにアストロサイトに由来するものかどうかは，今後の検討が必要である．

つぎに，海馬SGZで分裂・増殖した神経前駆細胞は幼若で未分化な神経細胞を経て成熟神経細胞に分化すると考えられる．海馬SGZにおいてBrdUでラベルされた細胞は，幼若神経細胞のマーカーであるpolysialylated neural cell adhesion molecule(PSA-NCAM)を発現することが，スナネズミ脳虚血モデルで認められている[10]．著者らは幼若神経細胞のマーカーであるdoublecortinが虚血侵襲後の海馬SGZでBrdUラベル1日後にすでに発現していることを認めている[6]．BrdUでラベルされた後，2週間以上を経て成熟神経細胞のマーカーであるNeuN，あるいは微小管結合蛋白質2(MAP2)を発現するようになり，神経前駆細胞由来の増殖細胞が神経細胞に分化する(図2)．

3. 虚血海馬での神経幹細胞分裂・増殖を規定する因子

これまでの報告で共通しているのが，海馬SGZでの増殖・分裂細胞数の増加は虚血後1週間以上を経てからピークに達するという点である．すなわち，虚血侵襲そのものが誘因というよりは，虚血によって引き起こされる二次的な因子がSGZ

サイドメモ　虚血脳にみられる内因性適応現象

脳神経細胞は虚血侵襲にとくに脆弱な細胞として知られているが，虚血ストレスに対していくつかの内因的な防御機構，あるいは修復機構が備わっている．神経細胞にあらかじめ非致死的な虚血負荷を加えておくと，その後に加わる本来致死的な虚血侵襲に対する抵抗性が増強する現象(虚血耐性現象)は著者らが最初に報告した現象であるが，神経細胞の適応現象の代表的なものである．そのメカニズムの解明も進み，CREB，NF-κBといった各種の転写因子の活性化を介した遺伝子発現の関与が明らかになってきた．しかし，いったん損傷を受けた脳組織に対する修復機構としては，本文で取り上げた神経細胞新生のほかにシナプス再生，神経回路網の再構築などが関与すると考えられている．このような脳組織が本来有する内因性の防御機構や修復機構を解明して最大限活用することが，脳血管障害のみならず各種の脳疾患に対する治療手段を進歩させるうえで肝要なことではなかろうか．

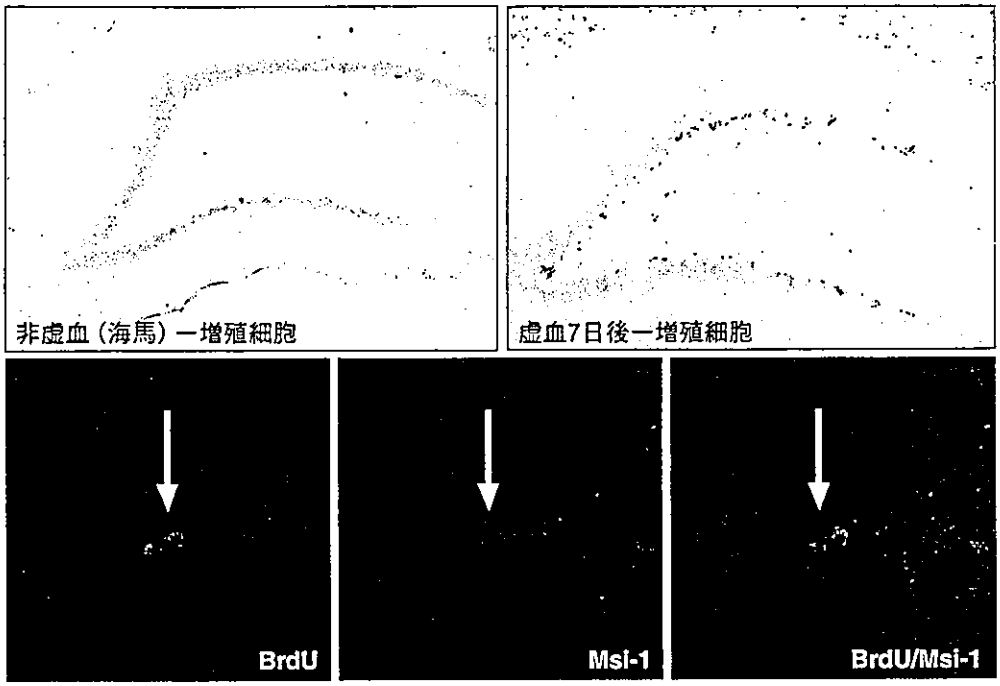

図 1　虚血海馬における神経前駆細胞の分裂・増殖の亢進

ラットに核酸チミジンのアナログである BrdU を投与して増殖細胞をラベルし，翌日に脳切片を作製し，免疫組織染色に供した．非虚血動物に比べ，虚血 7 日後の動物では海馬歯状回顆粒下層での BrdU 陽性細胞数の顕著な増加を認める．また，BrdU 陽性の増殖細胞の多くが神経前駆細胞の選択的マーカーである Musashi1(Msi-1)を発現している．

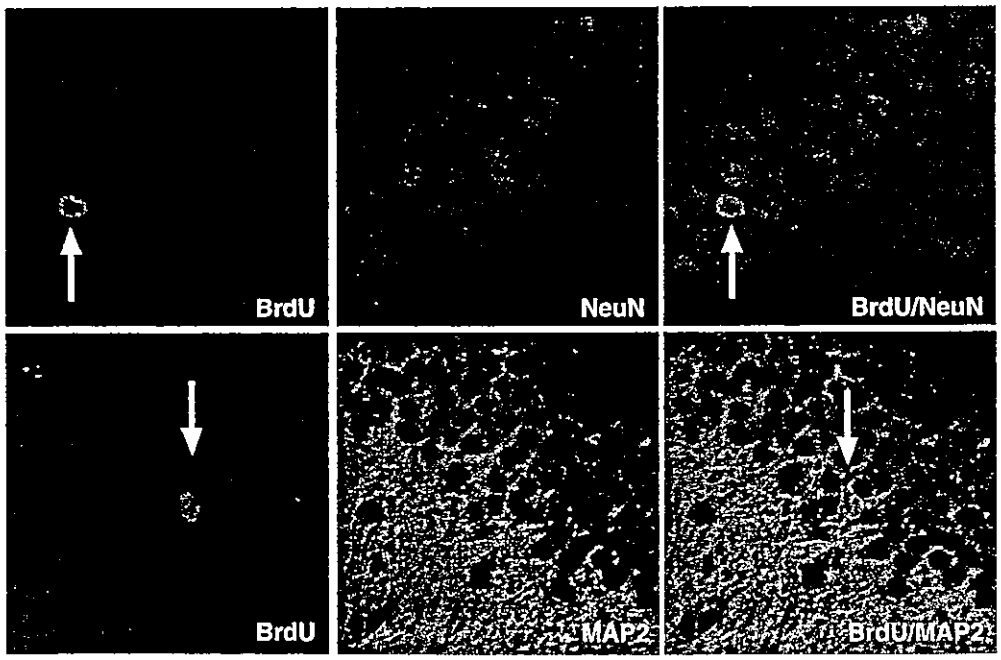

図 2　虚血海馬における増殖細胞の神経細胞への分化

ラット虚血 7 日後に BrdU を投与して増殖細胞をラベルし，1 カ月後に増殖細胞が神経細胞に分化していることを示す．海馬歯状回に存在する BrdU 陽性細胞は，成熟神経細胞のマーカーである NeuN および微小管結合蛋白質 2(MAP2)を発現している．

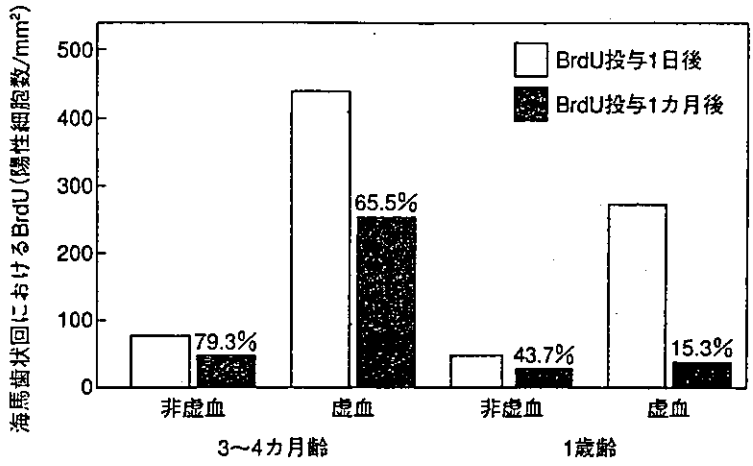

図 3　虚血海馬における神経細胞新生に対する加齢の影響

若年期(3〜4 カ月齢)と壮年期(1 歳齢)ラット海馬での BrdU でラベルされる増殖細胞数(BrdU 投与 1 日後および 28 日後)に対する虚血の影響を示す．%は BrdU 投与 1 日後に比べ 28 日後に生存した細胞の割合を示す．壮年期ラットでは若年齢ラットと同様に，虚血侵襲により BrdU 投与 1 日後にラベルされる増殖細胞数の顕著な増加を認めるが，いったん新生された細胞の 1 カ月後の生存率は若年齢(65.5%)に比べ，壮年期ラット(15.3%)では顕著に低下している．

での神経前駆細胞の分裂促進を規定していると考えられる．虚血をはじめとしたストレス直後には流血中にコルチコステロイドが放出され，神経細胞前駆細胞の分裂・増殖を抑制していると考えられる[11]．しかし，虚血後の海馬 SGZ の神経前駆細胞の動態はこれらの細胞が線維芽細胞成長因子(bFGF)などの投与により，速やかに分裂・増殖が促進されるのとは対照的である[12]．虚血海馬での規定要因としてもっとも有力視されているのが，虚血侵襲により二次的に分泌される神経栄養因子の関与である．bFGF を欠損させた動物では中大脳動脈閉塞後の海馬 SGZ での BrdU 陽性細胞数の増加が抑制されることが報告され，神経栄養因子の関与を示唆している[7]．また，グルタミン酸受容体拮抗薬[13,14]やアセチルサリチル酸[15]の投与によって虚血侵襲後の神経前駆細胞の分裂・増殖が抑制されることも報告されているが，その解釈は十分にされていない．また，虚血損傷によって神経回路網の破壊・再構築などもダイナミックに起こっており，それらの神経前駆細胞の分裂・増殖に及ぼす影響も想定される．

4. 虚血海馬での新生神経細胞生存維持に関与する因子

神経細胞新生を促進させるうえで，神経前駆細胞由来の分裂・増殖を促進させるのと並んで重要なのが，新生細胞の生存維持，神経細胞への分化促進である．生理的に豊かな環境，刺激の多い環境で飼育された動物は，神経前駆細胞の分裂程度には差がないものの，いったん分裂した細胞の生存維持が向上し，神経細胞新生に結びついている[16]．脳虚血モデルでの新生細胞生存維持に関しては著者らがラット一過性前脳虚血モデルで検討したのが最初である[9]．3〜4 カ月齢の若年成熟ラットでは正常海馬，虚血侵襲後の海馬いずれにおいても，BrdU 投与翌日にラベルされた増殖細胞の約 70〜80%は 1 カ月後にも生存し，神経細胞に分化しているのが観察されたが，1 歳齢の壮年期ラットでは虚血侵襲により BrdU 陽性の神経前駆細胞の分裂・増殖は同程度に生じるが，1 カ月後の生存が 20%以下と極端に低下し，結果的にはわずかな神経細胞新生にとどまることが明らかになった(図 3)[9]．また，ラット中大脳動脈閉塞モデルでは，3〜4 カ月齢の若年ラットであるにもかかわらず，反対側海馬で神経前駆細胞から分裂・増殖した細胞の生存率は 1 カ月後には 20%以下と顕著に低下しており，同モデルでの反対側海馬での神経細胞新生もわずかにとどまることが明らかとなった[6]．加齢ラット，虚血反対側海馬での新生

細胞の生存維持を低下させている要因は不明であるが，脳梗塞が壮年期から老年期に多い疾患であることを考えると，神経細胞新生の促進を臨床的な治療手段として考える場合，この点は解明，克服される必要がある．

側脳室下層での神経幹細胞動態，大脳皮質での神経細胞新生

成熟動物脳での神経幹細胞自体の性状に関する研究は，海馬 SGZ より側脳室下層(SVZ)でよく調べられている．生理的状態では SVZ での神経幹細胞が分裂・増殖して rostral migratory stream (RSM)を経由して嗅球に移動し，神経細胞に分化する．中大脳動脈閉塞モデルでは SVZ の近傍の大脳皮質や線条体が梗塞に陥るが，同側 SVZ での BrdU 陽性の増殖細胞数は海馬同様，虚血 7〜14 日後をピークとして増加している[4-7]．しかし，反対側 SVZ での BrdU 陽性細胞数に関しては虚血再灌流モデル[4]では同側と同様に BrdU 陽性細胞数が増加するが，永久閉塞モデル[5,6]では著者らの検討も含め，虚血後でもとくに大きな変動はなさそうである．しかし，虚血モデルでの SVZ での増殖細胞の性状に関する検討はされておらず，BrdU 陽性細胞のどの程度が神経幹または神経前駆細胞であるかは定かでない．また，虚血後に SVZ でみられる増殖細胞は近接した大脳皮質，線条体に移動して神経細胞に分化するのかどうかは明らかでない．しかし，同領域の神経幹細胞は脳室内に投与された神経栄養因子によく反応して増殖することから，脳梗塞周辺領域の神経細胞新生に寄与しうる可能性は高いと考えられる．

一方，脳梗塞モデルを用いて梗塞領域での神経細胞新生に関する研究も散見される[17,18]．しかし，脳梗塞およびその周辺領域では BrdU でラベルされる大部分の増殖細胞は，ミクログリア，マクロファージ，アストロサイトであり，神経細胞新生はないとする報告がある一方で，Wester らのグループは BrdU 陽性細胞のうち 3%に神経細胞のマーカーである MAP2 の発現がみられたと報告している．しかし，増殖した細胞が MAP2 を発現するには数日間という非常に短い期間であることや，損傷細胞への BrdU の取込みの可能性もあることから，その結果の解釈には注意を要する．脳梗塞モデルで梗塞周辺部で神経細胞新生が生じうるのか，また生じるとすればどの箇所の神経幹または神経前駆細胞に由来しているのかなど，明らかにされるべき点は多く残されている．

おわりに

虚血脳における神経前駆細胞の動態，その規定因子を明らかにすることは，脳梗塞に対する再生医学を応用した治療を開発するうえで必要不可欠の重要な事項であり，その現状について解説した．本稿では触れていないが，脳梗塞組織の神経細胞新生を促す手段として，神経前駆細胞や骨髄細胞を用いた体外からの細胞移植治療も試みられている．しかし，Parkinson 病における細胞移植とは異なり，脳梗塞で臨床的に神経機能の回復を期待するには，新生された神経細胞がもともと存在した神経細胞と同様なシナプス回路を形成する必要がある．虚血脳において神経回路網の再構築を伴った神経細胞新生を促すために，内因性の神経幹細胞からの分裂，増殖，分化，生存を最大限活用する手段の開発，進歩が望まれる．

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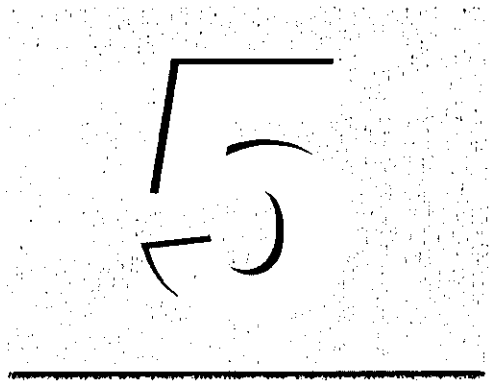

●脳血管障害

脳血管障害の重症度スケール

松本昌泰※ Matsumoto-Masayasu

はじめに

脳卒中の臨床診断に際して最も重要なことは，まず「脳卒中ではないか」と疑ってみることである．発症後3～6時間以内の超急性期治療の有効性が確立してきた現在，脳卒中初期症状への社会の認知度を高め，一刻も早い脳卒中専門医療機関への搬送を可能としなければならない．既に，米国では脳卒中をBrain Attack（脳発作）と呼び替え，その超急性期治療を推し進めるべく大衆への啓発キャンペーンを実施している[1]．その際には表1に掲げる5つの症状の1つ以上があればBrain Attackを疑い直ちに専門医療機関を受診することを勧めている．ただし，意識障害や言語障害などがあるときは患者本人が発症時の症状を訴えられないため，迅速に患者の状態を評価するとともに発症状況などを家人やその他の目撃者から聴取する必要がある．すなわち，救急の現場で働く看護スタッフはもちろんのこと，あらゆる医療スタッフが，医療現場以外で遭遇するBrain Attackへの対応について熟知し，心筋梗塞などの発症時と同様に迅速な判断を要求される時代に突入したといえる．

その意味で本稿では，まず始めに脳卒中の初期臨床診断に際して重要な問診や診察のポイントについて紹介し，その重症度評価に欠かせな

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表1　Brain Attackキャンペーンに用いられている脳卒中警告症状[1]

- 身体の片側の顔，腕，脚に突然脱力や痺れが出現する
- 突然目が見えなくなったり，物がぼやけて見える，特に片目に起こる
- 言葉が喋れなくなったり，話をしたり，理解するのが困難となる
- 突然の原因不明の激しい頭痛
- 訳の分からないめまい感，ふらつき感や突然の転倒，特に上記症状を伴う場合

表2　脳卒中の主要症状

意識障害 混迷，昏睡 錯乱状態	協調運動障害，筋力低下，感覚障害（通常片側性）
	平衡障害，失調症，歩行障害
失語症，その他の高次機能障害	筋力低下
構音障害	視野障害（単眼性もしくは両眼性）
顔面麻痺	複視，めまい，悪心，嘔吐，頭痛

い脳卒中重症度スケールについて紹介する．

脳卒中の有無とその重症度評価

表2には医師や看護スタッフが脳卒中を疑うべき主要な症状を掲げた．急性症状を有する患者が来院したときには，まずバイタルサインのチェックと気道・呼吸・循環確保などの応急処置を施し，その後，問診と神経学的検査を行う．

1　問診のポイント

どのようなときに（発症状況），どのように発症し（初発症候），どのような経過をたどっているか（症候の時間経過）を聞き出すのは問診上の重要ポイントである．また，脳卒中既往，家族歴，各種の危険因子（高血圧，糖尿病，心房細動など）や薬物服用歴（降圧薬，経口避妊薬など）などについての情報も病型や病態の診断上，極めて重要である．

脳卒中では一般に発症日時を特定できることが多く，特に脳出血，くも膜下出血，脳塞栓症などでは時間・分単位で発症日時を明らかにできる場合が多い．発症が，睡眠中などの安静時で大量飲酒の翌朝などの脱水を起こしやすい状況であった場合は血栓性機序による脳梗塞，身体活動時などの血圧上昇を来しやすい状況では脳出血やくも膜下出血，また活動開始直後などの循環動態急変時の発症では塞栓性機序による脳梗塞などが疑われる．

脳卒中の初発症候で最も頻度が高いのは，顔面を含む片麻痺や感覚障害であり，逆にこれらの症状が突然発症したときには，脳卒中を疑うのは容易である．言語障害では構音障害と失語症を区別する必要があり，後者では大脳皮質損傷を疑う．また，明らかな局所神経症候を呈さない突発性の激しい頭痛では，くも膜下出血が疑われ，悪心・嘔吐を伴うことが多く意識障害も起こる．片麻痺などの局所症候に引き続いて頭痛，悪心・嘔吐が見られる際には脳出血の可能性が高い．発作性めまいを伴う頭痛では，小脳出血や椎骨脳底動脈系梗塞を疑う必要がある．ただし，椎骨脳底動脈系の脳卒中の診断には，四肢の失調，感覚障害や，視野障害，構音障害，複視などの自覚症状の有無を詳細に確認する必要がある．

脳卒中を疑ったときに神経症候の時間経過（temporal profile）に注意することも極めて重要である．一過性脳虚血発作（transient ischemic

患者名：　　年齢：　歳　男・女　　発症日時：　/　/　時頃　　検査日：　/　/
診断名：　　麻痺側（右，左，両）　利き手（右，左，両）　　検者：

1．Level of consciousness（意識）

a) Glasgow Coma Scale

開眼（Eyes Open）	言語（Best Verbal Response）	運動（Best Motor Response）
4　自発的に開眼する	5　見当識良好	5　疼痛に適切に反応
3　呼びかけにより開眼する	4　混乱した会話	4　屈曲逃避
2　痛み刺激により開眼する	3　不適切な言葉	3　異常屈曲反応
1　まったく開眼しない	2　理解不能な応答	2　伸展反応（除脳姿勢）
	1　反応なし	1　反応なし

E+V+M=Total
（　）＋（　）＋（　）=□
A：15　B：14～7　C：6～3

□ A= 7.74
□ B=15.47
□ C=23.21

b) Japan Coma Scale

Ⅰ刺激しなくても覚醒している状態
9　まったく正常
8　大体意識清明だが，今1つはっきりしない（Ⅰ-1）
7　時・人・場所が分からない（見当識障害）（Ⅰ-2）
6　自分の名前，生年月日が言えない（Ⅰ-3）

Ⅱ刺激すると覚醒する状態
5　普通の呼びかけで容易に開眼する（Ⅱ-10）
4　大きな声または体を揺さぶることにより開眼する（Ⅱ-20）
3　痛み・刺激を加えつつ呼びかけを繰り返すとかろうじて開眼する（Ⅱ-30）

Ⅲ刺激しても覚醒しない状態
2　痛み刺激に対し払いのける様な動作をする（Ⅲ-100）
1　痛み刺激で少し手足を動かしたり顔をしかめる（Ⅲ-200）
0　痛み刺激にまったく反応しない（Ⅲ-300）

A：9　　B：8～3　　C：2～0

2．Language（言語）

1. □頭命令で拳を作る（両側麻痺の場合は□頭命令で開眼する）
2. 時計を見せて“時計”と言える
3. “サクラ”を繰り返して言える
4. 住所，家族の名前が上手に言える

A：4/4　　B：3/4or2/4　　C：1/4or0/4（None）

□ A=1.47
□ B=2.95
□ C=4.42

3．Neglect（無視）（可能な限り裏面の線分を使用のこと）

A. 線分二等分試験正常
B. 線分二等分試験で半側空間無視
C. 麻痺に気が付かない．あるいは一側の空間を無視した行動をする

□ A=0.42
□ B=0.85
□ C=1.27

図1　脳卒中重症度スケール（Japan Stroke Scale：JSS）[2]
本スケールの使用法は，①各項目の該当カテゴリーを選ぶ，②これに基づいてA，B，Cのいずれかを選び右側にある該当の枠にチェックを入れる，③チェックの入った枠の右側に示されている数字を合計する，④最後にconstantの値－14.71を加える，⑤以上の計算で得られた数値が重症度スコアでおおよそ－0.38と26.95の間の値を取る．なお，実際のカードには裏面に長さ25cmの太線が印刷してあり，無視の評価に用いるようになっているが，誌面の都合上省略した．

4. Visual Loss or Hemianopia（視野欠損または半盲）
   A. 同名性の視野欠損または半盲なし
   B. 同名性の視野欠損または半盲あり
   ☐ A=0.45
   ☐ B=0.91

5. Gaze Palsy（眼球運動障害）
   A. なし
   B. 側方視が自由にできない（不十分）
   C. 眼球は偏位したままで反対側へ側方視できない（完全共同偏視または正中固定）
   ☐ A=0.84
   ☐ B=1.68
   ☐ C=2.53

6. Pupillary Abnormality（瞳孔異常）
   A. 瞳孔異常（対光反射and/or瞳孔の大きさの異常）なし
   B. 片側の瞳孔異常あり
   C. 両側の瞳孔異常あり
   ☐ A=1.03
   ☐ B=2.06
   ☐ C=3.09

7. Facial Palsy（顔面麻痺）
   A. なし
   B. 片側の鼻唇溝が浅い
   C. 安静時に口角が下垂している
   ☐ A=0.31
   ☐ B=0.62
   ☐ C=0.93

8. Plantar Reflex（足底反射）
   A. 正常
   B. いずれとも言えない
   C. 病的反射（BabinskiまたはChaddock）陽性（1回でも認められたら陽性）
   ☐ A=0.08
   ☐ B=0.15
   ☐ C=0.23

9. Sensory System（感覚系）
   A. 正常（感覚障害がない）
   B. 何らかの軽い感覚障害がある
   C. はっきりした感覚障害がある
   ☐ A=−0.15
   ☐ B=−0.29
   ☐ C=−0.44

10. Motor System（運動系）（臥位で検査する）

Hand（手） A：1 B：2or3 C：4or5
   1. 正常
   2. 親指と小指で輪を作る
   3. そばに置いたコップが持てる
   4. 指は動くが物はつかめない
   5. まったく動かない
   ☐ A=0.33
   ☐ B=0.66
   ☐ C=0.99

Arm（腕） A：1 B：2or3 C：4or5
   1. 正常
   2. 肘を伸ばしたまま腕を挙上できる
   3. 肘を屈曲すれば挙上できる
   4. 腕はある程度動くが持ち上げられない
   5. まったく動かない
   ☐ A=0.66
   ☐ B=1.31
   ☐ C=1.97

Leg（下肢） A：1 B：2or3 C：4or5
   1. 正常
   2. 膝を伸ばしたまま下肢を挙上できる
   3. 自力で膝立てが可能
   4. 下肢は動くが膝立てはできない
   5. まったく動かない
   ☐ A=1.15
   ☐ B=2.31
   ☐ C=3.46

TOTAL= ☐

CONSTANT −14.71

SCORE= ☐