確認事項

- 発症時刻(最終未発症確認時間)
- 治療開始(予定)時刻3時間以内
- 症状の急速な改善がない
- 軽症(失調、感覚障害、構音障害、軽度の麻痺のみを呈する)でない

禁忌

既往歴
- 頭蓋内出血既往
- 3ヵ月以内の脳梗塞(TIAは含まない)
- 3ヵ月以内の重篤な頭部脊髄の外傷あるいは手術
- 21日以内の消化管あるいは尿路出血
- 14日以内の大手術あるいは頭部以外の重篤な外傷
- 治療薬の過敏症

臨床所見
- 痙攣
- くも膜下出血(疑)
- 出血の合併(頭蓋内出血、消化管出血、尿路出血、後腹膜出血、喀血)
- 頭蓋内腫瘍・脳動脈瘤・脳動静脈奇形・もやもや病
- 収縮期血圧(適切な降圧後も185mmHg以上)
- 拡張期血圧(適切な降圧後も110mmHg以上)

血液所見
- 血糖異常(50mg/dL以下、400mg/dL以上)
- 血小板100,000/mm^{3}以下
- ワーファリン内服中、PT-INR 1.7以上
- ヘパリン投与中、APTTの延長(前値の1.5倍以上または正常範囲を超える)
- 重篤な肝障害
- 急性膵炎

画像所見
- CTで広汎な早期虚血変化
- CT/MRI上の圧排所見(正中構造偏位)

慎重投与(適応の可否を慎重に検討する)

既往歴
- 10日以内の生検・外傷
- 10日以内の分娩・流早産
- 3ヵ月以上経過した脳梗塞
- 蛋白製剤アレルギー

臨床所見
- 年齢75歳以上
- NIHSS スコア23以上
- JCS 100以上
- 消化管潰瘍・憩室炎、大腸炎
- 活動性結核
- 糖尿病性出血性網膜症・出血性眼症
- 血栓溶解薬、抗血栓薬投与中
- 月経期間中
- 重篤な腎障害
- コントロール不良の糖尿病
- 感染性心内膜炎

〈注意事項〉

- 確認事項は完全に満足する必要がある。
- 一項目でも「禁忌」に該当すれば実施しない。
- 一項目でも「慎重投与」に該当すれば、適応の可否を慎重に検討し、治療を実施する場合でも「リスクとベネフィット」を患者本人・家族に正確に説明し同意を得る必要がある。

表4　アルテプラーゼ静注療法のチェックリスト
(文献25, p334より引用)

である。表3に本指針の冒頭で特に強調されている注意事項を、表4にチェックリストにあげられた項目を列挙し、図3に本療法のアルゴリズムを再掲しておく。わが国のチェックリスト(表4)は米国での治療適応患者(表2)と完全には一致していない。わが国では、独自に「慎重投与」の項が設けられ、医師判断や患者・家族同意を重視した形となっている。

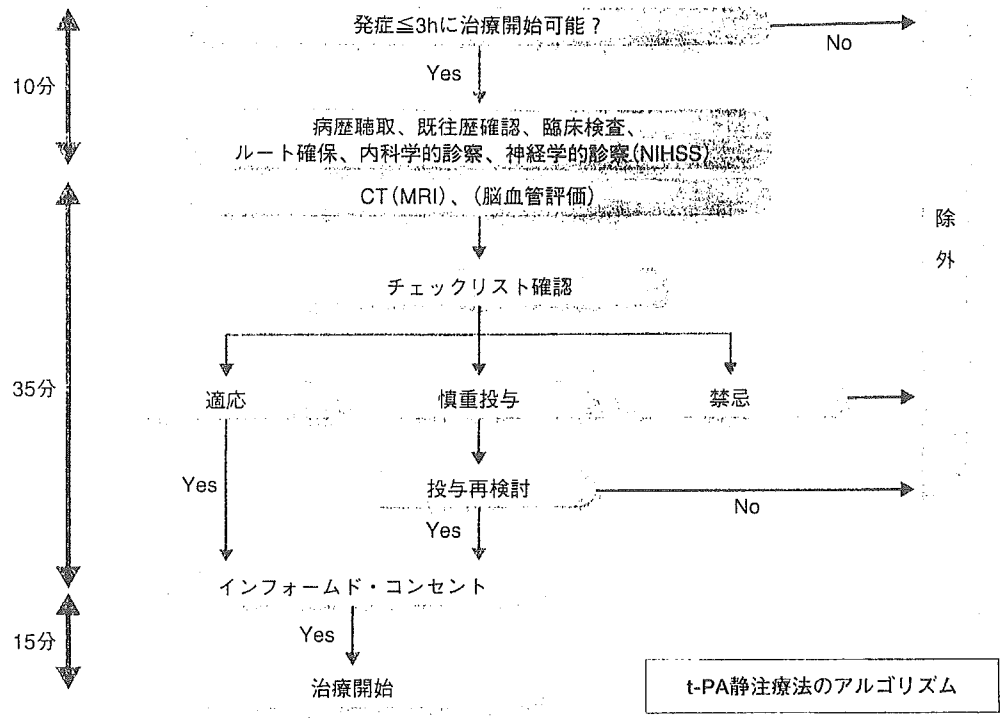

図3　アルテプラーゼ静注療法のアルゴリズム(文献2、p341より引用)

①患者を適応例、慎重投与例、禁忌例に分けること、②迅速な評価、適応判断、インフォームドコンセントを行い、来院から60分以内に治療を開始することがポイントとなる。

同年10～12月にかけて、販売会社2社と日本脳卒中学会の共催で、全国各都道府県で「適正治療指針」の周知徹底を目的とした「適正治療講習会」が各3～4回ずつ開催された。なお、日本脳卒中学会医療向上・社会保険委員会が提案するrt-PA静注療法の施設基準には、①24時間体制のCT/MRI検査、②集中治療のための十分な人員と設備、③脳外科的処置が迅速に実施可能であることとともに、④治療実施施設の担当者が原則として講習会を受講しておくことが銘記されている。

新しい血栓溶解療法の試み

rt-PA(アルテプラーゼ)が米国で承認されてからもうすぐ10年目を迎える。欧米ではすでに、次の段階を目指した試みが盛んである。

1．経頭蓋超音波照射併用療法

超音波照射が血栓溶解効率を向上させることは、実験的あるいは臨床的に示唆されてきた。Alexandrovら[9]は、発症3時間以内の急性中大脳動脈閉塞63例に対し、アルテプラーゼ投与直

後より2-MHzの診断用経頭蓋ドプラ（transcranial Doppler；TCD）の連続照射を併用し、再開通率や転帰をアルテプラーゼ投与のみの63例と比較検討した。その結果、2時間後の完全再開通＋臨床症候劇的改善は後者で有意に高率であり、発症3ヵ月後の転帰良好（mRSスコア0～1）も42％対29％と併用群で良好な傾向があった（p＝0.2）。

より低周波の装置を用いた試験が欧州でも行われたが、頭蓋内出血発生が高頻度で、試験は中止された[25]。わが国では、慈恵医大グループを中心に照射＋診断一体型血栓溶解療法専用TCDが開発され、検討が進められている。

2．第三世代血栓溶解薬とMR技術

発症後3時間以降でもペナンブラ領域が残存していれば、血栓溶解療法の効果が期待できる。Hackeら[10]は、最新のMR技術でdiffusion-perfusion mismatch（ペナンブラ領域を示唆）の検出された発症後3～9時間の患者を対象に、第3世代血栓溶解薬デスモテプラーゼ（desmoteplase）を投与する第Ⅱ相RCTを実施した。その結果、用量依存性の再開通率向上と転帰良好例増加が認められたという。現在、本格的な第Ⅲ相RCTが計画されている。

おわりに

rt-PA静注療法の臨床応用競争においてわが国は、かって世界最先端にあったが、1995年以降は競争から完全に離脱してしまった。この間世界40ヵ国以上で、東アジアでも韓国、台湾、中国、シンガポールなどでアルテプラーゼが承認されている。このたび、わが国でもやっとアルテプラーゼ静注療法が承認されたが、承認後2.5年間にわたる全例調査（調査予定3,000例以上）という厳しい条件が付されている。いわば仮免許状態である。承認とほぼ同時の治療指針の公表、全都道府県における複数回の講習会開催など、国内では過去例のない事態が続いている。

一方で、J-ACTの結果を受けて、0.9mg/kgという従来の画一的な投与量が果たして妥当であるのか、少なくとも東アジアでは至適投与量を見直すべきではないのかという議論も巻き起こっている。rt-PA静注療法のさらなる治療成績向上や適応患者拡大において、わが国が世界的貢献を果たすことも不可能ではないと思われる。カムバック、ジャパン！

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Risk factors for occlusive lesions of intracranial arteries in stroke-free Japanese

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The aim of this study was to identify relevant risk factors for occlusive lesions of the intracranial arteries in stroke-free population. The subjects of this study were 425 patients without a history of stroke or transient ischemic attack and without any abnormality on a neurological examination who consecutively visited a neurology clinic between January 1994 and June 2001 requesting medical evaluation for possible cerebrovascular diseases. Subjects included 245 men and 180 women ranging in age from 33 to 89 years (mean ± SD = 64.0 ± 10.0 years). We performed cervical and intracranial magnetic resonance angiography (MRA) in all subjects. Using a validated rating scheme of MRA for occlusive lesions, we evaluated the degree of stenoses in the extracranial portion of the internal carotid artery (ICA) and the intracranial arteries including the intracranial portion of the ICA, middle cerebral artery (MCA) stem, intracranial portion of the vertebral artery (VA), and basilar artery (BA). More than 25% stenoses were regarded as significant lesions in this study. Multiple logistic regression analyses showed that significant and independent predictors for extracranial ICA lesions were age, hyperlipidemia, and ischemic heart disease (IHD), those for intracranial ICA lesions were age, hypertension, diabetes mellitus, and IHD, those for MCA lesions were age and hypertension, those for intracranial VA lesions were hyperlipidemia and IHD, and those for BA lesions were hypertension and diabetes mellitus. The present study suggested that atherosclerosis of the intracranial VA was related to hyperlipidemia and IHD as was the case for the extracranial carotid artery, whilst atherosclerosis of other sites of intracranial arteries was associated with hypertension and diabetes mellitus in stroke-free Japanese.

Introduction

In a previous study of stroke-free subjects using magnetic resonance angiographies (MRAs) (Uehara *et al.*, 1998), we found that the risk factors for occlusive lesions in the cervical carotid artery and intracranial arteries were different. Age and hyperlipidemia were risk factors for the former, and age and hypertension were risk factors for the latter. In that study we categorized the basilar artery (BA) into a common group of intracranial arteries together with the intracranial internal carotid artery (ICA) and the middle cerebral artery (MCA). However, some investigators (Caplan *et al.*, 1986; Yasaka *et al.*, 1993) have suggested that, in patients with ischemic stroke or transient ischemic attack (TIA), risk factors for BA lesions differ from those for MCA lesions. According to Caplan *et al.* (1986), extracranial ICA and BA lesions belong to a group closely related to hyperlipidemia and coronary heart disease, whilst MCA lesions belong to another group related to hypertension but not to hypercholesterolemia. They also pointed out that the intracranial ICA and the intracranial vertebral artery (VA) did not fall clearly into any of these groups because of a lack of information for these vessel sites (Caplan *et al.*, 1986). Yasaka *et al.* (1993) demonstrated that, in patients with ischemic stroke or TIA, MCA trunk atherosclerosis was related to advanced hypertension, and that atherosclerosis of both the BA and the extracranial ICA was associated with high serum lipid levels, coronary heart disease, and diabetes mellitus. However, until now, no studies have been carried out to examine risk factors for occlusive lesions in each site of the intracranial arteries in stroke-free subjects. We therefore looked for regional differences in the risk factors for occlusive lesions of the intracranial arteries in Japanese without stroke by using MRA.

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Materials and methods

Subjects

Subjects of this study were recruited from outpatients without stroke or TIA who consecutively visited the

clinic of the neurology service in our hospital between January 1994 and June 2001. All the patients without any history of stroke or TIA episode who requested medical evaluation for possible cerebrovascular diseases because of reasons including a simple fear of stroke, positive family history of stroke, vascular risk factors, and non-specific subjective symptoms such as headache or dizziness, and without a contraindication for magnetic resonance imaging (MRI) were invited to the study. Informed consent for the study was obtained from all the patients. Patients were carefully checked for their medical history and given a complete neurological examination, and cranial MRIs were employed. Patients whose examination was indicative of stroke or those whose scans revealed incidental significant lesions (except for asymptomatic lacunar infarcts in white matter, basal ganglia, or thalamus) were excluded (nine patients). Patients with migraine (four patients) and those with vertigo possibly caused by brainstem or cerebellar dysfunction (five patients) were not included in this study. Finally, the subjects of this study were 425 patients, including 245 men and 180 women ranging in age from 33 to 89 years (mean ± SD =64.0 ± 10.0 years). One hundred and fifty-six of these subjects also participated in the previous study (Uehara *et al*:, 1998).

Magnetic resonance angiography examinations

All MRA examinations were performed with a 1.0 tesla MR system (Magnetom Impact; Siemens, Erlangen, Germany). Image acquisition and reconstruction are described elsewhere (Uehara *et al.*, 1994, 1995). The extracranial portion of the ICA was evaluated based on the carotid MRA. The intracranial portion of the ICA, the horizontal portion of the MCA, the intracranial portion of the VA, and the BA were evaluated based on the intracranial MRA. Two investigators (T.U. and M.T.), who were blinded to all clinical information, independently reviewed the MRAs and rated occlusive lesions for each arterial portion into five grades depending on the narrowness of the arteries (Uehara *et al.*, 1994, 1995): <25% reduction of an arterial diameter was graded as normal, 25–49% reduction was graded as mild stenosis, 50–74% reduction was graded as moderate stenosis, 75–99% reduction was graded as severe stenosis, and no opening was graded as occlusion. When the judgment of the two readers was inconsistent, a decision was entrusted to a third investigator (E.M). To measure the percent stenosis of the extracranial portion of the ICA, we compared the diameter of maximal stenosis with that of the normal-appearing proximal ICA beyond the carotid bulb [North American Symptomatic Carotid Endarterectomy Trial (NASCET) Steering Committee, 1991]. Aplasia or hypoplasia of the VA is not uncommon, in which MRA assessment of stenosis is impractical. We regarded as VA aplasia/hypoplasia when fulfilled the followings: (i) the diameter of the VA in the dominant side being not smaller than the diameter of the BA, (ii) a smooth transition from the dominant VA to the BA, and (iii) the VA of the non-dominant side being not visible, constantly narrow through the whole length or terminated into the posterior inferior cerebellar artery.

The accuracy of MRA in detecting occlusive disease of extra- and intra-cranial ICA system was previously shown to be high (Uehara *et al.*, 1994, 1995). An additional validation study was carried out to evaluate the accuracy of MRA for the vertebrobasilar artery system, comparing MRA with conventional angiography. Subjects of this validation study consisted of 58 patients (44 men and 14 women, mean ± SD =60.7 ± 11.3 years old) selected from those who were admitted to our hospital for suspected ischemic cerebrovascular diseases (45 patients with ischemic stroke, 10 patients with TIA, two patients with cervical bruit, and one patient with transient global amnesia) between April 1992 and December 1993 and were given both MRA and conventional angiography studies within 1 month of each other. Seven vessels of the VA, which showed hypoplasia on both MRA and conventional angiography, were excluded because they were unable to estimate the degree of stenosis. The Spearman rank correlation coefficients between the conventional angiography rating and the MRA rating were 0.86 for the VA, 0.89 for the BA, and 0.80 for the posterior cerebral artery (PCA). When considering the normal-abnormal dichotomy, the sensitivity was 100% for the VA, 100% for the BA, and 83.3% for the PCA. The specificity was 93.9% for the VA, 96.0% for the BA, and 83.7% for the PCA. Because PCA lesions were uncommon, this portion was not considered in this study. Moreover, the proxymal portion of the VA was not also taken into consideration in this study, as the origin of the VA, a common site of occlusive lesions, was unable to evaluate on the cervical MRA.

Risk factors

Hypertension, diabetes mellitus, hyperlipidemia, smoking habit, and ischemic heart disease (IHD) were evaluated as risk factors. Hypertension was judged as present when either a systolic pressure of >140 mmHg or a diastolic pressure of >90 mmHg was demonstrated on repeated examinations or when a history of treatment for hypertension was present. Diagnosis of diabetes mellitus was made when the fasting blood glucose level was >126 mg/dl or when a history of treatment for diabetes mellitus was present. Hyperlipidemia was judged as present when laboratory

examination of the serum at presentation showed a high total cholesterol level of >220 mg/dl, a high triglyceride level of >150 mg/dl, a low high-density-lipoprotein cholesterol level of <40 mg/dl, or when a history of treatment was present. Smoking habit included previous history of smoking. IHD was defined as a known history of myocardial infarction or angina pectoris.

Statistical analyses

Multiple logistic regression analyses were used to estimate independent effects of the predictive variables on the cerebral arterial occlusive lesions. The contrast was between those with and without lesion in each site. All statistical analyses were carried out with StatView software (SAS Institute Inc., Cary, NC, USA). The level of significance was set at $P < 0.05$ for all statistical analyses.

Results

Two hundred five subjects (48.2%) were hypertensive, 91 subjects (21.4%) were diabetic, and 113 subjects (26.6%) were hyperlipidemic. One hundred thirty-nine subjects (32.7%) had a smoking habit. IHD was positive in 109 subjects (25.6%).

The results of MRA findings are summarized in Table 1. For estimation of MRA findings, the rate of agreement between two readers (T.U. and M.T.) was 94.6% (kappa = 0.92). Four vessels of the intracranial ICA and five vessels of the MCA were not assessable because of occlusion in their proximal portion. For the VA, 48 vessels were not assessable because of hypoplasia. Bilateral lesions were found in the extracranial ICA in 11 subjects, in the intracranial ICA in three subjects, in the MCA in two subjects, in the intracranial VA in two subjects. Fifteen subjects had both extracranial and intracranial lesions.

Table 1 Magnetic resonance angiography findings

	Extracranial	Intracranial			
Stenosis rating[a]	ICA	ICA	MCA	VA	BA
Normal	384	398	398	409	416
Mild stenosis	26	16	21	9	6
Moderate stenosis	7	7	0	3	1
Severe stenosis	4	3	5	3	2
Occlusion	4	1	1	1	0
Abnormal (%)[b]	9.6	6.4	6.4	3.8	2.1

[a]Based on the rating of more affected side in case of bilateral vessel lesions.
[b]Stenoses of more than 25%.
ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery.

Multiple logistic regression analyses showed that significant and independent predictors for lesions were age, hyperlipidemia, and IHD for the extracranial ICA, age, hypertension, diabetes mellitus, and IHD for the intracranial ICA, age and hypertension for the MCA, hyperlipidemia and IHD for the intracranial VA, and hypertension and diabetes mellitus for the BA (Table 2).

Discussion

Multiple logistic regression analyses showed that significant and independent predictors of the extracranial ICA lesions were age, hyperlipidemia and IHD, and

Table 2 Predictors for stenoses

Variable	Odds ratio	95% confidence interval	*P*-value
Extracranial ICA			
Age (>65 years)	2.67	1.30 5.48	0.0074
Male sex	1.88	0.93 3.79	0.0782
Hypertension	1.62	0.84 3.11	0.1492
Diabetes mellitus	1.37	0.66 2.86	0.3982
Hyperlipidemia	2.38	1.23 4.60	0.0099
Smoking habit	1.70	0.89 3.27	0.1110
Ischemic heart disease	3.95	2.05 7.64	<0.0001
Intracranial ICA			
Age (>65 years)	5.36	1.82 15.85	0.0024
Male sex	2.08	0.85 5.06	0.1069
Hypertension	5.01	1.85 13.55	0.0015
Diabetes mellitus	4.05	1.81 9.08	0.0007
Hyperlipidemia	2.14	0.95 4.80	0.0664
Smoking habit	1.55	0.69 3.48	0.2847
Ischemic heart disease	2.25	1.00 5.07	0.0496
MCA			
Age (>65 years)	3.36	1.33 8.51	0.0105
Male sex	0.91	0.42 2.00	0.8203
Hypertension	6.96	2.37 20.51	0.0004
Diabetes mellitus	1.90	0.82 4.38	0.1331
Hyperlipidemia	1.69	0.75 3.80	0.2084
Smoking habit	1.23	0.55 2.75	0.6206
Ischemic heart disease	1.78	0.79 4.01	0.1662
Intracranial VA			
Age (>65 years)	2.02	0.69 5.93	0.1984
Male sex	3.31	0.93 11.78	0.0651
Hypertension	2.49	0.85 7.29	0.0967
Diabetes mellitus	2.25	0.80 6.37	0.1256
Hyperlipidemia	13.39	3.74 47.95	<0.0001
Smoking habit	2.12	0.78 5.78	0.1410
Ischemic heart disease	6.98	2.37 20.59	0.0004
BA			
Age (>65 years)	7.41	0.92 59.77	0.0601
Male sex	1.48	0.37 6.00	0.5822
Hypertension	9.07	1.12 73.15	0.0385
Diabetes mellitus	7.67	1.88 31.32	0.0045
Hyperlipidemia	2.25	0.59 8.55	0.2322
Smoking habit	1.03	0.25 4.18	0.9677
Ischemic heart disease	1.46	0.36 5.95	0.5956

that those of the MCA lesions were age and hypertension. These findings were well consistent with the findings of previous studies (Heyden *et al.*, 1970; Crouse *et al.*, 1986, 1987; Salonen *et al.*, 1988; Craven *et al.*, 1990; Handa *et al.*, 1990; Howard *et al.*, 1990; Tanaka *et al.*, 1993; Yasaka *et al.*, 1993; Fabris *et al.*, 1994; Fine-Edelstein *et al.*, 1994; Uehara *et al.*, 1998). Heyden *et al.* (1970), who analyzed a group of patients with angiographically documented non-embolic cerebral artery occlusion, noted that patients with extracranial carotid lesions had a high frequency of associated IHD and hypercholesterolemia. Several ultrasonography studies have shown that extracranial carotid lesion is related to hyperlipidemia (Crouse *et al.*, 1987; Salonen *et al.*, 1988; Handa *et al.*, 1990; Fabris *et al.*, 1994; Fine-Edelstein *et al.*, 1994) and IHD (Crouse *et al.*, 1986, 1987; Craven *et al.*, 1990; Howard *et al.*, 1990; Tanaka *et al.*, 1993).

Although there have been fewer studies of MCA lesions than of extracranial ICA lesions, the results of the present study were consistent with those in the previous studies (Heyden *et al.*, 1970; Yasaka *et al.*, 1993; Uehara *et al.*, 1998; Takahashi *et al.*, 1999). Caplan *et al.* (1986) suggested that very common hypertension and relatively uncommon hypercholesterolemia could explain a predilection for occlusive lesions of the MCA and a low prevalence of occlusive extracranial ICA disease and coronary artery disease in Japanese. Yasaka *et al.* (1993) concluded that advanced hypertension was related to MCA trunk atherosclerosis. Takahashi *et al.* (1999) reported that hypertension and high serum levels of glycosylated hemoglobin A1c were significant and independent predictors of atherosclerotic lesions of the MCA detected by MRA in Japanese.

Like the MCA lesions, the intracranial ICA lesions had age, hypertension, and diabetes mellitus as significant and independent predictors. In addition, we found a weak but significant correlation between intracranial ICA lesions and IHD. Ingall *et al.* (1991) demonstrated that significant and independent predictors of intracranial ICA atherosclerosis found by conventional angiography were duration of cigarette smoking, age, hypertension, and diabetes mellitus. Marzewski *et al.* (1982), who followed up >66 patients with more than 50% stenosis of the intracranial ICA for an average of 3.9 years, concluded that intracranial ICA stenosis was a marker of extensive cerebrovascular and systemic atherosclerotic disease, especially coronary artery disease. Little is known about the risk factors for intracranial ICA occlusive lesions.

In the present study, atherosclerosis of the intracranial VA was related to hyperlipidemia and IHD as was the case for the extracranial carotid artery, whilst atherosclerosis of BA was associated with hypertension and diabetes mellitus. Our results clearly suggested that intracranial VA lesions belong to the same class as extracranial ICA lesions, which are closely related to hyperlipidemia and IHD. Although no studies comparable to the present study have examined the risk factors for intracranial VA occlusive lesions, the New England Medical Center Posterior Circulation Registry (Muller-Kuppers *et al.*, 1997; Shin *et al.*, 1999) reported that the prevalences of hypertension, hyperlipidemia, diabetes mellitus, smoking, and IHD were high in patients with symptomatic intracranial VA occlusive lesions. In addition, the prevalence of coronary artery disease in patients with symptomatic intracranial VA occlusive disease was reportedly quite high, ranging from 20 to 36% (Bogousslavsky *et al.*, 1986; Moufarrij *et al.*, 1986; Muller-Kuppers *et al.*, 1997; Shin *et al.*, 1999), which supports our findings. However, our results failed to verify the previous view. Caplan *et al.* (1986), in a review of occlusive cerebrovascular disease, found that atherosclerosis of the large arteries including extracranial ICA and BA, was closely related to hyperlipidemia and coronary artery disease. Yasaka *et al.* (1993) demonstrated that atherosclerosis of extracranial ICA and BA was strongly associated with high serum lipid levels, coronary heart disease, and diabetes mellitus in patients with ischemic stroke. This discrepancy may be attributable to the different characteristics of the cohorts, a difference between patients with ischemic stroke and stroke-free subjects, or to the small number of subjects with BA stenosis. In the present study, the proxymal segment of the VA was not studied, as it was not accessible on the cervical MRA we used. As the origin of the VA is a critical site, risks for the proxymal VA lesions should be elucidated in future.

Finally, limitations of the present study have to be mentioned. The subjects of this study were patients without a history of stroke or TIA and without any abnormality on a neurological examination who visited a neurology service requesting medical evaluation for possible cerebrovascular diseases. To minimize the selection bias as far as possible, subjects of this study were prospectively recruited from consecutive outpatients. The cohort in the present study is a part of stroke-free general population. However, this kind of study is prone to referral or selection bias. The prevalence derived from such a hospital-based study should be carefully interpreted and applied to general population. Nevertheless, at least the association between risk factors and vascular lesions demonstrated could be generalizable, as the association would be universal. Another weakness is that the individual lesion numbers were all low, which may introduce type II errors. The ideal study method is to conduct a population-based study rather than a hospital-based study,

and larger population-based studies are evidently needed to confirm our findings. Low prevalence also affects the creditability of the MRA rating results. False positives, which may unavoidably occur in MRA, are of concern especially in a low-risk population. The most vulnerable site for MRA is the intracranial ICA, where the false positive rate is considerably high. Signal discontinuity caused by tortuosity of the vessel in this region would be often judged as 'severe' stenosis (Uehara *et al.*, 1994). However, in the present study, as the occasion of 'severe' rating was very few, most of the stenotic ratings should be true.

In conclusion, the present study suggested that atherosclerosis of the intracranial VA was related to hyperlipidemia and IHD as was the case for the extracranial carotid artery, whilst atherosclerosis of other sites of major intracranial arteries was mainly associated with hypertension and diabetes mellitus in stroke-free Japanese. Our results might shed light into the important question why there were ethnic differences in the distribution of atherosclerotic lesion. In the future, a study investigating the correlation between the severity of the occlusive lesions and risk factors is needed to determine the predictors of the development of atherosclerosis.

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Trigeminal neuralgia due to pontine infarction

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An 85-year-old man with diabetes mellitus suddenly developed dysesthesia over the left side of the face, which persisted for a few months and then disappeared. Two years later, he experienced intermittent lancinating pain in the territory of the maxillary branch of the left trigeminal nerve triggered by brushing teeth and chewing. Neurologic examination disclosed slightly diminished superficial sensation in the territory of the maxillary branch of the left trigeminal nerve. MRI revealed a tiny wedge-shaped lesion in the pontine base consistent with an old infarction, which has affected the intramedullary portion of the left trigeminal root (figure). Pontine infarction is believed to cause trigeminal neuralgia,[1,2] and this case documents a clear relationship between the trigeminal root entry zone lesion and trigeminal neuralgia.

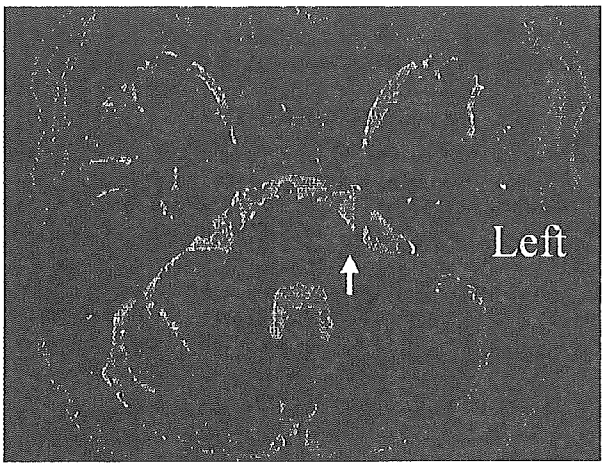

Figure. T2-weighted MRI superimposed on a three-dimensional constructive interference in the steady state image revealing a tiny wedge-shaped lesion in the pontine base consistent with an old infarction (white arrow), which has affected the intramedullary portion of the left trigeminal root. Black arrow indicates the left trigeminal nerve.

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第3回北海道ブレインアタックフォーラム

急性期脳梗塞の画像診断：CTを中心に

佐々木真理*

要　旨：拡散強調画像によって急性期脳梗塞の検出能は大幅に向上したが，血栓溶解療法における意義は十分に確立していない。頭部単純CTの果たす役割は大きいが，撮影法・表示法や判定法を吟味し，初期虚血変化の診断能向上を図る必要がある。CT灌流画像はMR灌流画像に比し定量性など利点が多いが，検査被曝の低減や解析結果の信頼性向上が急務である。CTもしくはMRI単独で迅速に必要充分な情報を取得することが理想だが，現時点では両者とも課題が多い。

Key words：急性期脳梗塞，頭部単純CT，early CT signs，CT灌流画像，マルチスライスCT

はじめに

MRI，とりわけ拡散強調画像（diffusion-weighted image: DWI）の出現によって急性期脳梗塞の画像診断は飛躍的進歩を遂げた。DWIと灌流強調画像（perfusion-weighted image: PWI）を主軸とした複合的MRI検査は広く受け入れられ，多くの施設で用いられている。しかしながら，MRI全盛の現在においても，血栓溶解療法（薬事未認可）の治療適応基準のスタンダードは未だ頭部CTとされている[1,2]。これは主にMRIのavailabilityの低さと科学的根拠の不足に起因すると思われる。本稿では，急性期脳梗塞のCT診断についてMRIと比較しながら解説することで，両者の特徴を明らかにするとともに，今後の検査戦略のありかたを考えていきたい。

頭部単純CT

血栓溶解療法の適応決定において頭部単純CTは重要な役割を果たしている。CTでは，出血性病変の否定の他，初期虚血変化（early CT signs）の判定が重要である[3]。Early CT signsは，レンズ核の不明瞭化，皮髄境界の不明瞭化，脳溝の狭小化 を指し，患者予後や重大合併症の予測因子であることが知られている（図1）。Early CT signsが無いかごく軽微である場合，血栓溶解療法の適応となる[1,2]。MRIでは同種の基準は未だ確立していない。

前方循環系の心原性脳塞栓症では，early CT signsはDWIと同時期，同範囲に出現することが多く，T2強調画像，FLAIR画像より鋭敏である。ただし，ラクナ梗塞や後方循環系の梗塞では無力である。Early CT signsは軽微な変化なため，DWIに比べ客観性が劣る。熟練度によって診断能が異なること，判定者間格差が大きいことが知られている[4]。また，画質によって描出能が大きく左右されるため，撮影条件や表示条件には細心の注意を払う必要がある[3]。局所線溶療法のランダム化比較試験（RCT）であるMELT-Japan（MCA-embolism local fibrinolytic intervention trial）では，CTの撮影法，表示法，判定法を標準化することで，early CT signsの診断能向上を達成している（http://melt. umin.ac.jp）。なお，MDCTは一般に画質面で不利なため，撮影条件には特に配慮する必要があるが，最近ではMDCTならではの高画質化技術が登場しつつある。

Makoto Sasaki: CT imaging in acute stroke.
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図1　頭部単純CTの初期虚血変化（early CT signs）とASPECTS
左中大脳動脈閉塞，発症1.5時間。
左島皮質の不明瞭化（白矢頭），皮質領域の皮髄境界の広汎な不明瞭化（黒矢頭）を認める。本所見のみで，血栓溶解療法の適応外であること，予後が不良であることがわかる。
Early CT signsがI，M1～M6領域に認められるので，ASPECTSは3点となる。

Early CT signsの範囲判定に関する基準の中では，“中大脳動脈領域の1/3以下”（1/3 MCA rule）が有名である。これは多くのRCTなどで採用されているが，具体的な判定法は公開されておらず，客観的尺度としては問題が多いことが指摘されている。より客観的なものとしてASPECTS（Arberta stroke program early CT score）がある[5]。代表的な2断面において中大動脈領域を10区域に分けスコア化した平易なもので，読影者間一致率が高いことが知られている（**図1**）。

その他，頭部単純CTでは新鮮な塞栓子を高吸収領域として検出できる場合がある（hyperdense MCA sign）[6]。しかし検出率が1/3程度と低く，MRIのflow void消失やFLAIRのintraarterial signalに比べ明らかに劣る。なお，出血の否定に関しては，MRI T2*強調画像でCTを代替可能であることが報告されているが[7]，同時に検出される無症候性微小出血などをどのように扱っていくのかは今後の課題である。

CT灌流画像

CT灌流画像（CT perfusion: CTP）はヨード造影剤を血管内トレーサとして用いる脳循環検査である。MDCTでは多断面撮影が可能なことと解析ソフトの性能向上によって普及しつつある。CTPはMRI PWIと原理を同じくするが，実際には異なる点も多い[8]。CTPはPWIに比べ空間分解

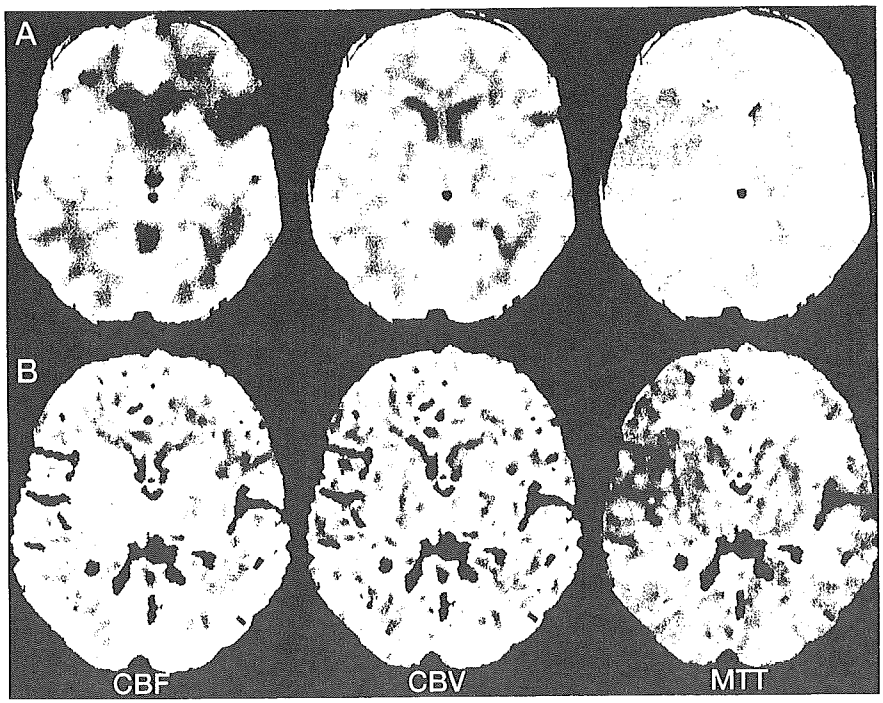

図2　急性期脳梗塞のCT灌流画像
左中大脳動脈分枝閉塞，発症3時間。
左中大脳動脈前枝領域の広汎なMTTの遅延，左前頭弁蓋部のCBFの低下を認める。
同一データにおいても，解析ソフトによって定量値や画質は大きく異なる（A, B）

能や造影増強効果の線形性が高く，動脈入力関数の取得も容易である。そのため，PWIでは困難な脳血流量（cerebral blood flow: CBF）などの定量値を算出することができる。頭部単純CTに引き続き短時間で施行できる点も魅力である。一方，検査被曝が大きいこと，撮影範囲がMDCTでも20～40mmと狭いことが問題であるが，被曝に関しては種々の被曝低減技術によって通常の2～5倍程度まで減少した。

CTPの解析手法としては，PWIと異なり，deconvolution法を用いるのが一般的である。脳組織の時間濃度曲線を動脈入力関数で逆畳込演算して平均通過時間（mean transit time: MTT）を，時間濃度曲線下面積（area under the curve: AUC）を静脈で補正して脳血液量（cerebral blood volume, CBV）を求め，Meierのcentral volume theoremに則り，CBVをMTTで除してCBFを求めることが多い。解析上の課題は，元画像の画質，deconvolution法の種類，ノイズ除去フィルタの種類や強さ，血管除去法の有無や種類，動脈入力関数の取得部位などによって解析結果が大きく変動する点である[8,9]。現時点では装置間・施設間の差異はあまりに大きく，同一環境における安定性も低いため，普遍的な指標とはなりがたい（**図2**）。ただし，国内でCTPの標準化作業が進行しており，既に一定の成果を挙げつつある（http://ctp.umin.jp）。近い将来安定した脳循環検査技術となることが期待される。なお，PWIでも従来のAUCや重心法MTTといった定性解析に替わり，deconvolution法による定量解析が試みられつつあるが，CTPの解析上の問題点は全てPWIにも当てはまることを忘れてはならない。

急性期脳虚血の重症度は残存CBFと虚血の持続時間に依存する。CBFが一定以下に低下すると脳組織は可逆的な酸素代謝障害（ischemic penumbra）に陥り，低下の程度に応じて刻一刻と非可逆的な虚血，即ち梗塞に移行する[10]。梗塞に陥った組織は血栓溶解療法などによる血行再開通によって救済できないばかりか，むしろ症候性出血などの重大合併症を引き起こす危険が増加する。従って，脳循環検査によって虚血の重症度を判定することで，患者予後向上に寄与できる可能性がある。とりわけ，血栓溶解療法の有効性が証明されていない発症3時間以降の適応決定に役立つと考えられており，即時性の高いCTP, PWIに対する期待は大きい[11]。

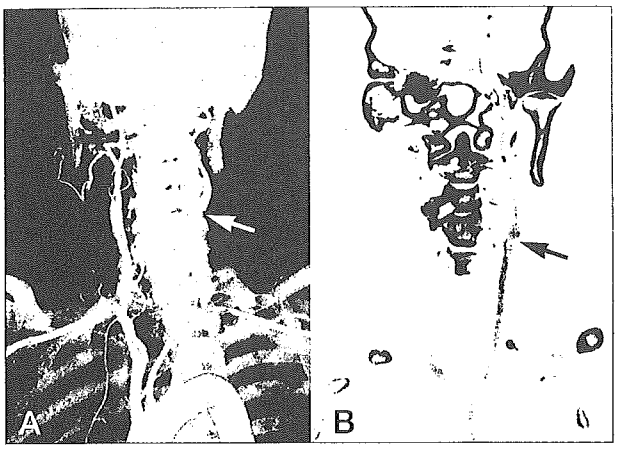

図3　64列MDCTによる頸部血管CTA
左内頸動脈狭窄，撮影時間8秒。A: volume rendering, B: curved planar reconstruction（白黒反転）。大動脈弓から頭蓋内血管までの良好な画像が得られている。短時間で撮影が終了しているため，静脈の重なりが殆ど無い。左頸動脈分岐部に潰瘍形成を伴う狭窄を認める（矢印）。
（藤田保健衛生大学放射線医学教室　片田和廣先生のご厚意による）

虚血の重症度判定法には，Xe-CTやSPECTによる定量値，半定量値（対側比，小脳比）があり，重大合併症や患者予後の予測因子としての意義が既に確立している[11]。一方，MRIではdiffusion-perfusion mismatchが普及しているが，penumbraとの乖離がある，閾値判定ではなく領域判定である，CBFを利用できない，灌流異常の指標にコンセンサスが得られていない，治療適応基準が確立していない，患者予後向上への寄与を示唆する科学的根拠に乏しい　など課題も多い。それに対し，CTPではCBFを容易に得ることができるため，Xe-CT, SPECTと同様の閾値による重症度判定が可能となる。また，最近ではCBV-CBF mismatch（prognostic map）といった閾値と領域の両者の情報をもつ指標も提唱されており[12]，解析技術の進歩や標準化の推進によって信頼性・安定性が担保できるようになれば，近い将来標準的な検査となる可能性がある。

CTA

CTで脳血管の情報を得るには，造影剤を用い

たCTAを施行せねばならないが，実際にはCTPに引き続き短時間で検査を行うことができる。造影剤はCTPで40mL程度，CTAで60mL程度を用いればよく，総使用量は通常と変わらない。CTAでは頭蓋底や石灰化がしばしば狭窄病変判定の障害となるが，近年の画像処理法の進歩によってこれらの問題は克服されつつある。最新型の64列MDCTではCTAの画質は飛躍的に向上する。大動脈弓から頭蓋内までを0.5mm厚でほんの7～8秒でカバーできるため，静脈の重なりのない精緻な画像をえることができ，超音波検査と同等以上の頸部血管病変の評価が可能となると思われる(図3)。

おわりに

急性期脳梗塞の画像診断についてCTの最近の動向を中心に述べた。血栓溶解療法のtherapeutic time windowの極端な狭さを考慮すると，単一の検査で短時間に複合的情報が得られることが理想である。現時点では，CT, MRIのどちらか1つを施設の状況に応じて選択することが妥当と思われる。しかし，両者とも多くの課題を抱えており，まずそれらを解決していかねばならない。そのためには検査の標準化，科学的根拠の創出，ガイドラインの策定を平行して進めていく必要があり，それによって真に患者の予後向上に寄与する検査としての意義を確立できると考える。

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