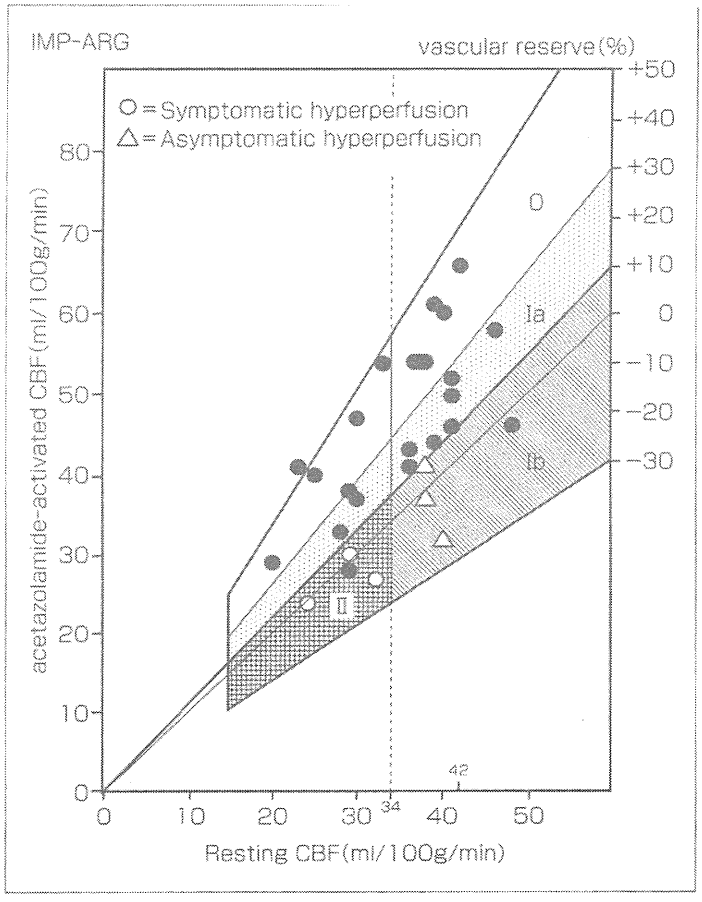

図 5.
CEA 症例における術前血行力学的脳虚血の重症度評価と術後過灌流との関係
症候性過灌流は，血行力学的脳虚血 stage Ⅱであった 4 例中 3 例に，無症候性過灌流は，血行力学的脳虚血 stage Ⅰのうちで脳循環予備能が 10%以下(stage Ⅰb)であった 4 例中 3 例に認められた．

ドライン 2009 では，CEA の適応については次のように推奨されている[5]．① 症候性頚動脈高度狭窄(>70%，NASCET 法)では，抗血小板療法を含む最良の内科的治療に加えて，手術および周術期管理に熟達した術者と施設において頚動脈内膜剝離術を行うことが推奨される(グレード A)．② 症候性頚動脈中等度狭窄では，抗血小板療法を含む最良の内科的治療に加えて，手術および周術期管理に熟達した術者と施設において頚動脈内膜剝離術を行うことが推奨される(グレード B)．③ 無症候性頚動脈高度狭窄では，抗血小板療法を含む最良の内科的治療に加えて，手術および周術期管理に熟達した術者と施設において頚動脈内膜剝離術を行うことが推奨される(グレード B)．④ 症候性頚動脈軽度狭窄あるいは無症候性中等度ないし軽度狭窄において，頚動脈プラークの不安定化や潰瘍形成が認められる場合は，頚動脈内膜剝離術を行うことは考慮してもよいが，それを行うことに十分な科学的根拠はない(グレード C1)．一方，米国 American Heart Association(AHA)がまとめた脳梗塞予防ガイドラインによると，治療適応の条件としては狭窄度のみならず外科治療の周術期リスク(morbidity and mortality)が明確に規定され，症候性頚動脈狭窄の場合には 6%以下，無症候性頚動脈狭窄の場合には 3%以下であることが必要とされている[13]．

一方，頚動脈狭窄症の脳循環動態に関するこれまでの研究によると，CEA 術前に CO_2 またはアセタゾラミドに対する脳血管反応性の低下あるいは脳循環予備能の低下がみられる症例では，術後にこれらの指標の改善が得られるが[14]，これらの指標が高度に低下した症例では CEA 術後に過灌流症候群(hyperperfusion syndrome：頭痛や片麻痺，痙攣で発症する脳出血，術後約 1%に生じる)などの周術期リスクが高まることが知られ[15]，高度の血行力学的脳虚血がみられる症例では CEA の high-risk 群として対応しなければならない．脳血流 SPECT 定量によって診断される血行力学

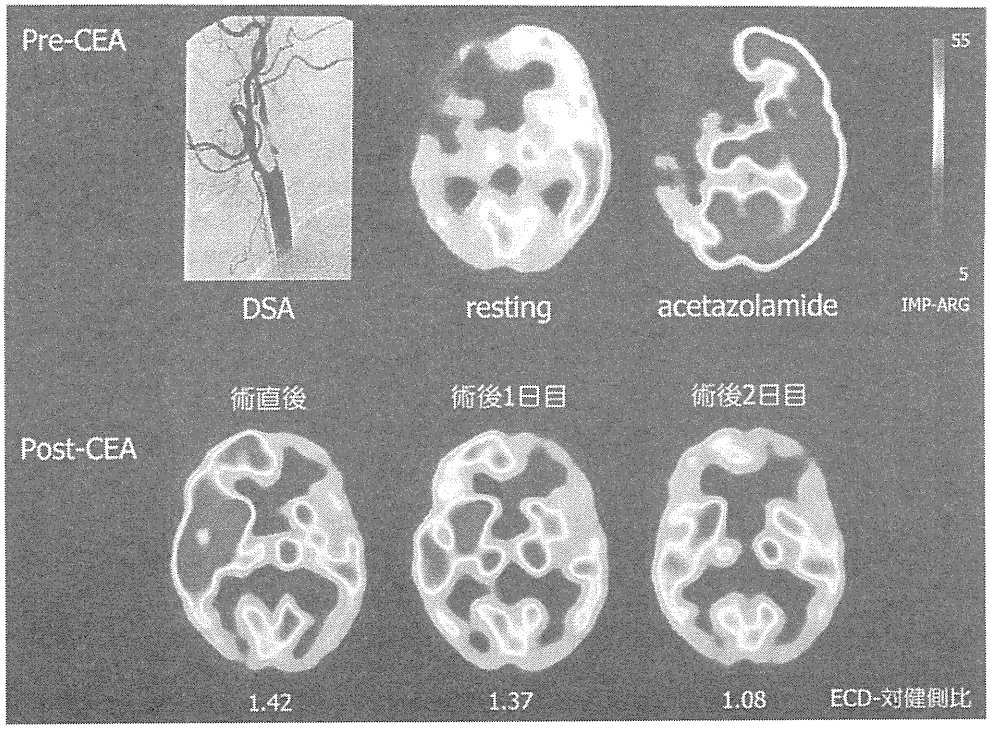

図 6. CEA 術後過灌流症候群の SPECT 画像

72 歳，男性．一過性脳虚血発作にて発症した右頚動脈狭窄症に対して再発予防を目的とした CEA が施行された．術前の安静時脳血流 SPECT およびアセタゾラミド負荷時脳血流 SPECT の定量解画像により，右内頚脳動脈領域は血行力学的脳虚血 stage Ⅱ と判定された（上段）．術直後の ECD-SPECT では，右内頚脳動脈領域に過灌流（対健側比 1.42）が認められ，全麻下での管理が継続された．術後 1 日の ECD-SPECT では過灌流（対健側比 1.37）がみられたが，術後 2 日の ECD-SPECT では，過灌流が消退した（対健側比 1.08）（下段）．

的脳虚血 stage Ⅱ は，症候性頚動脈狭窄症群の 20%，無症候性頚動脈狭窄症群の 8%に認められ，これらの症例では術後高率に無症候性の高灌流を併発する（図 5）[15]．したがって，stage Ⅱ は CEA の high-risk 群と考えられ，周術期管理が重要となる．Stage Ⅱ と診断された場合には，術中の脳保護対策として軽度低体温麻酔や内シャントチューブの使用などを考慮する必要がある．また，術後には高灌流症候群を予測し，全身麻酔下での SPECT 検査と集中治療室での対応策をあらかじめ準備すべきである（図 6）．

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Cerebral Microbleeds in Patients with Moyamoya-like Vessels Secondary to Atherosclerosis

Makiko Tanaka, Manabu Sakaguchi, Kaori Miwa and Kazuo Kitagawa

Abstract

Objective Hemorrhagic risk is unknown in patients with moyamoya-like vessels associated with atherosclerotic intracranial cerebral artery occlusion. This study was undertaken to investigate the association between moyamoya-like vessels and cerebral microbleeds (CMBs) in patients with atherosclerotic steno-occlusive disease.

Methods The study population comprised 34 patients with steno-occlusive lesions in the intracranial cerebral artery caused by atherosclerosis. We evaluated the presence of moyamoya-like vessels at the base of the brain by cerebral angiography, and the presence of CMBs by T2*-weighted MRI. Patients were divided into 2 groups: those with and those without moyamoya-like vessels; clinical histories and the incidence of CMBs were compared between the groups.

Results Sixteen patients had moyamoya-like vessels. Twelve of 16 patients with moyamoya-like vessels had a history of ischemic stroke or transient ischemic attack, whereas only 1 patient had a history of symptomatic cerebral hemorrhage. The incidence of CMBs did not differ between the 2 groups (31% vs. 28%, p=0.82). The location of CMBs varied and was not associated with the site of moyamoya-like vessels.

Conclusion CMBs were not associated with moyamoya-like vessels in patients with atherosclerotic cerebral artery occlusion. These patients may not have a high risk of cerebral hemorrhage.

Key words: atherosclerosis, cerebral microbleeds, moyamoya phenomenon, magnetic resonance imaging, intracranial hemorrhage

(Intern Med 51: 167-172, 2012)
(DOI: 10.2169/internalmedicine.51.6429)

Introduction

Moyamoya disease is characterized by chronic, progressive, bilateral stenosis of the terminal portion of the internal carotid arteries or its proximal branches, with no known cause, and it leads to the formation of an abnormal vascular network composed of collateral pathways (moyamoya vessels) at the base of the brain (1, 2). In adult patients, moyamoya disease frequently manifests with sudden-onset intracranial hemorrhage (3, 4). Hemorrhage is assumed to be the result of the collapse of fragile moyamoya vessels by hemodynamic loading and rupture of the peripheral aneurysms that are often formed on moyamoya vessels (5). Several studies showed that the incidence of cerebral microbleeds (CMBs) in adult patients with moyamoya disease, as detected by gradient-recalled echo (GRE) T2*-weighted magnetic resonance imaging (MRI), is higher than that in healthy individuals, indicating that multiple CMBs are a predictor of subsequent hemorrhage in these patients (6-8).

Moyamoya-like vessels, which also mean abnormal vascular networks at the base of the brain, are associated with cerebrovascular steno-occlusive disease caused by atherosclerosis and this condition is distinguished from moyamoya disease (9-11). The risk of intracranial hemorrhage in patients with moyamoya-like vessels secondary to atherosclerosis is unknown, although these patients frequently receive antithrombotic agents. The aim of this study was to investigate the association between basal moyamoya-like vessels and CMBs in patients with intracranial cerebral artery occlusion by atherosclerosis.

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Received for publication August 21, 2011; Accepted for publication September 28, 2011
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Table 1. Clinical History of the Patients (n=34)

Age (years), mean ± SD	61.4 ± 11.1
Sex (M/F, N)	22/12
Hypertension, N	29
Diabetes, N	13
Dyslipidemia, N	27
Current smoking, N	9
Stroke or TIA, N	27
Occlusive vascular lesion	
Middle cerebral artery	29
Anterior cerebral artery	8
Carotid siphon	6

TIA; transient ischemic attack

Materials and Methods

Patients

In all, 62 patients with intracranial steno-occlusive arteries, and with less than 50% stenosis in the extracranial carotid arteries, underwent cerebral digital subtraction angiography for clinical assessment of the cerebral artery, between March 2000 and June 2010 at our department. All patients had 1 or more intracranial arterial stenosis≥75% or occlusion. T2*-weighted GRE MRI data were available for 51 of the 62 patients. Given our focus on moyamoya phenomenon caused by atherosclerosis, we excluded patients with cerebrovascular occlusion of unknown origin, including patients with moyamoya disease or suspected moyamoya disease (n=12), patients with cerebral angiitis (n=1), and patients with other autoimmune disease (n=2). Patients who had undergone extracranial-to-intracranial arterial bypass surgery (n=2) were also excluded. The remaining 34 patients (22 men and 12 women, 38-74 years old) were included in the study. The cause of the intracranial stenosis or occlusion was clinically presumed to be atherosclerotic in all patients, based on the clinical manifestation, the presence of atherosclerotic cerebrovascular changes in other areas, and 1 or more atherosclerotic risk factors. Most of the patients had steno-occlusive lesions in the stem of the middle cerebral artery (Table 1); some patients had more than 1 steno-occlusive lesion. The study group included 27 symptomatic and 7 asymptomatic patients. The symptomatic patients had a history of transient ischemic attack (n=8), minor ischemic stroke (n=18), or intracranial hemorrhage (n=1). In the asymptomatic patients, including those who had non-focal symptoms such as dizziness or headache, the stenotic lesions were detected incidentally by MR angiography. We evaluated their angiographic and MRI data, and their clinical histories. All study protocols were approved by the Ethics Committee for Clinical Research in our institute.

Imaging

All patients underwent digital subtraction angiography for clinical purposes. Angiographic information included the site of steno-occlusive lesion and the presence of moyamoya-like vessels on the side of the occluded artery (Fig. 1). The presence of moyamoya-like vessels at the base of the brain was assessed by 2 investigators in the arterial phase images.

All MR examinations were performed on a 1.5 T imager (Signa, GE Healthcare, Milwaukee, WI) with a commercially available head coil. The subject was supine, with the neck and head in the neutral position. Axial T2*-weighted GRE sequences were obtained (repetition time / echo time, 600 / 20 ms; flip angle, 20°; matrix, 256×256; field of view, 220 mm; slice thickness, 5 mm). At the same time, axial T 1-weighted sequences and axial T2-weighted sequences were acquired to distinguish CMBs from the signal voids of cerebral arteries and from other mass lesions with hemorrhage, such as cavernous angiomas. Fluid-attenuated inversion recovery sequences were acquired to evaluate subcortical and deep white matter lesions.

CMBs were defined as homogeneous, round, hypointense lesions (<10 mm in diameter) in the brain parenchyma on GRE MRI (12). Macrobleeds were distinguished from microbleeds, i.e., lesions with a diameter of≥10 mm on GRE MRI were distinguished as macrobleeds. Hypointense lesions within the subarachnoid space, and areas of symmetrical hypointensity in the globus pallidus on GRE, were considered to represent adjacent pial blood vessels or calcifications, and were excluded. The presence and location of CMBs were assessed independently by 2 trained observers blinded to all clinical information about the subjects. When results differed between the evaluators, the decision was made after consulting a third evaluator.

Subcortical and deep white-matter lesions were evaluated using a rating scale (0-3) devised by Fazekas et al, and were defined as positive when the white-matter lesions were scored as 2 or 3 (13).

Statistical analyses

All analyses were performed with JMP 8.0.2 (SAS Institute Inc., Cary, NC). Based on the presence or absence of basal moyamoya-like vessels, the patients were classified into 2 groups. The presence of CMBs, presence of white-matter lesions, and clinical histories were compared between the groups. The patients were also divided into 2 groups according to the presence or absence of CMBs, and clinical variables were compared between the groups. We used Mann-Whitney's U test for continuous data and the χ^2 test for categorical data. Fisher's exact test (2-tailed) was used in place of the χ^2 test for categorical data when the number of cells was less than 5. Probability values<0.05 were considered significant.

Results

Of the 34 patients, 16 patients had moyamoya-like vessels. Twelve of 16 (75%) patients with moyamoya-like vessels and 14 of 18 (78%) patients without moyamoya-like vessels had a history of ischemic stroke or transient ischemic attack. Only 1 patient with moyamoya-like vessels had a history of symptomatic cerebral hemorrhage (Table 2).

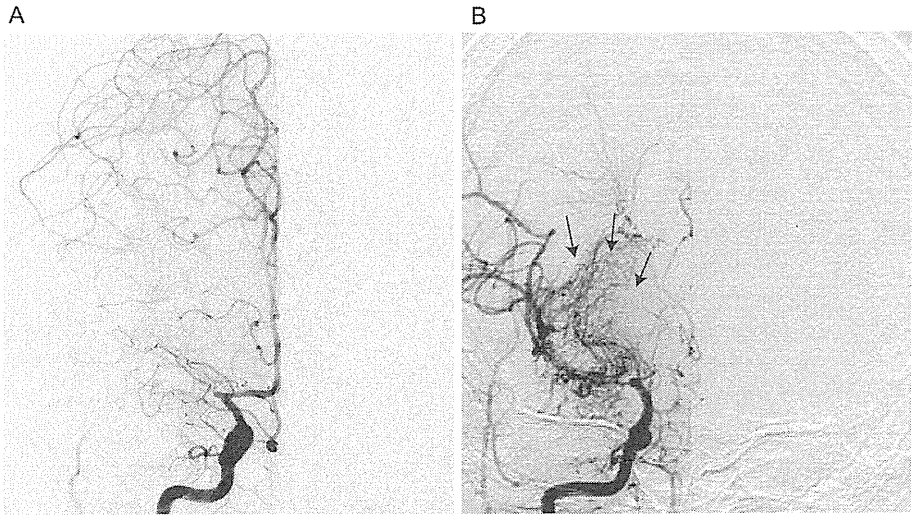

Figure 1. Representative angiographic images in patients with and without moyamoya-like vessels. A; anteroposterior image of a patient with right middle cerebral artery occlusion. No apparent moyamoya-like vessels at the base of the brain are visualized. B; anteroposterior image of a patient with moyamoya-like vessels. The arrows indicate moyamoya-like vessels at the base of the brain.

Table 2. Stroke Subtypes of Patients with and without Moyamoya-like Vessels

	Moyamoya-like vessels (+) n = 16	Moyamoya-like vessels (-) n = 18
Atherothrombotic	6	10
Lacunar	1	1
Transient ischemic attack	5	3
Cerebral hemorrhage	1	0
Asymptomatic	3	4

Table 3. Clinical Histories of Patients with and without Moyamoya-like Vessels

	Moyamoya-like vessels (+) n = 16	Moyamoya-like vessels (-) n = 18	p
N	16	18	
Age (years), mean ± SD	64.2 ± 7.9	58.8 ± 13.0	0.39
Male, %	50.0	77.8	0.09
Cerebral microbleeds, %	31.3	27.8	0.82
Hypertension, %	87.5	83.3	1.00
Diabetes, %	31.3	44.4	0.41
Dyslipidemia, %	87.5	72.2	0.41
Current smoking, %	12.5	38.9	0.13
Ischemic heart disease, %	31.3	5.6	0.08
Stroke or TIA, %	81.3	77.8	1.00
Antithrombotic drugs, %	75.0	83.3	0.68

TIA; transient ischemic attack

Ten patients had CMBs, 1 had asymptomatic cerebral macrobleeds, and 1 had symptomatic bleeding. The incidence of asymptomatic CMBs did not differ between patients with and without moyamoya-like vessels (31% vs. 28%, p=0.82). The patients with moyamoya-like vessels included a higher proportion of women (p=0.09) and patients with ischemic heart disease (p=0.08) (Table 3). Meanwhile, the presence of white-matter lesions appeared to be related to the presence of CMBs. Other clinical factors were not associated with the presence of CMBs (Table 4).

Table 5 shows the location and number of CMBs or macrobleeds and angiographic findings in each patient. In the group with moyamoya-like vessels, two patients had CMBs located close to the moyamoya-like vessels (Patient 2 and Patient 4) and the others had CMBs away from the moyamoya-like vessels.

Table 4. Variables Relevant to Cerebral Microbleeds

	CMB(+)	CMB(-)	p
N	10	24	
Age	61.7 ± 13.5	61.3 ± 10.3	0.64
Male, %	70.0	62.5	1.00
Hypertension, %	80.0	87.5	0.62
Diabetes, %	50.0	33.3	0.36
Dyslipidemia, %	90.0	75.0	0.64
Current smoking, %	20.0	29.2	0.69
Ischemic heart disease, %	20.0	16.7	1.00
Stroke or TIA, %	80.0	79.2	1.00
Antithrombotic drugs, %	70.0	83.3	0.39
Deep white matter lesion, %	60.0	29.2	0.13
Moyamoya-like vessels, %	50.0	45.8	0.82

CMB, cerebral microbleed; TIA, transient ischemic attack

Table 5. Number and Location of Cerebral Microbleeds/Macrobleeds and Angiographic Findings

No.	Age and sex	Cerebral microbleeds and macrobleeds		Angiographic findings
		Location	Total number	
Moyamoya-like vessels (+)				
1	65 M	Bil thalamus	2	R M1 O, L A2 S, R basal MM
2	70 F	R putamen	1	R M1 O, R A2 S, R basal MM
3	72 M	R temporal subcortex	1	R M1 O, R basal MM
4	73 M	L frontal cortex	1	Bil carotid siphon O, Bil expansive MM
5	69 M	R temporal subcortex	1	L M1 O, L carotid siphon S, L basal MM
6	50 M	R frontal subcortex (30 mm, symptomatic)	1	R M1 O, R basal MM
Moyamoya-like vessels (-)				
7	62 M	L thalamus, L para lateral ventricle	2	L M1 O
8	55 M	Pons, Bil thalamus, putamen, and corona radiata	14	L M1 S, L A1 O
9	74 F	R parieto-occipital subcortex, R thalamus	2	R M1 S
10	58 M	L thalamus, L putamen	3	L M1 S, L A1 S
11	39 F	Bil thalamus	2	L M1 S
12	72 M	L caudate nucleus (15 mm, asymptomatic)	1	L M1 O

M; male, F; female, R; right, L; left, Bil; bilateral, O; occlusion, S; stenosis, MM; moyamoya-like vessels

Discussion

CMBs have a prevalence of 5.7% and are observed more frequently with advancing age (14). The Rotterdam Scan Study determined that the prevalence of CMBs was 17.8% in the general population aged 60-69 years and 38.3% in those over 80 years old (15). The prevalence of CMBs is also much higher in patients with ischemic stroke than in the healthy population (34% vs. 5%) (16). CMBs are particularly associated with hypertensive small vessel diseases. Among the stroke subtypes, the incidence of CMBs is significantly greater in patients with intracerebral hemorrhage and patients with lacunar infarction than in patients with cardioembolic infarction, patients with atherothrombotic infarction, or healthy individuals (17). The prevalence of CMBs was 29.4% in our subjects. The subjects of the present study had a mean age of 61.4 years, and most had a history of ischemic stroke or transient ischemic attack. The prevalence of CMBs was not high compared to the reported prevalence in elderly patients with ischemic stroke.

CMBs are also detected in patients with adult moyamoya disease. The reported prevalence of CMBs was 15-44% and it varied according to MRI resolution (6, 7). However, the

mean age of those subjects was in the early 40s, indicating that those subjects were much younger than most patients with hypertensive small vessel diseases. According to the histopathological findings, fragile moyamoya vessels were indicated to be the cause of CMBs (18). Moreover, multiple CMBs in adult moyamoya disease were reported to be a risk factor for subsequent intracranial hemorrhage (8). CMBs can be considered a marker for the risk of intracranial hemorrhage in moyamoya disease.

We showed here that CMBs were not associated with the site of basal moyamoya-like vessels caused by atherosclerotic steno-occlusive cerebral arteries, and that the prevalence of CMBs did not differ in patients with moyamoya-like vessels and patients without moyamoya-like vessels. CMBs in our patients were presumed to represent the microangiopathy ordinarily caused by atherosclerosis, and its pathology may not be the same as that of CMBs in adult moyamoya disease.

In our subjects, the history of symptomatic cerebral hemorrhage was scarce, but the prevalence of ischemic events was high. In the previous reports of patients with moyamoya-like vasculopathy from atherosclerotic occlusive disease, most patients presented with cerebral ischemia and cerebral hemorrhage was rare (10, 11, 19-21). Moyamoya-like vessels may be less likely to be associated with the risk of cerebral hemorrhage in atherosclerotic occlusive disease than in adult moyamoya disease. Medical therapies are not effective for moyamoya disease. The frequencies of ischemic and hemorrhagic stroke are both high in adults whose moyamoya disease is treated conservatively (22-24). However, patients with atherosclerotic intracranial occlusive artery should receive antithrombotic treatment on the basis of individual hemorrhagic risks despite the presence of moyamoya-like vessels.

The reason for the differing hemorrhagic risk between adult moyamoya disease and moyamoya phenomenon secondary to atherosclerosis is not clear. Differing features of these 2 diseases are the site of the occlusive major cerebral arteries and the age at onset. Collateral vessels, including extensive moyamoya vessels, develop alongside progressive occlusive changes in the terminal portion of the internal carotid arteries in adult moyamoya disease. Moyamoya phenomenon secondary to atherosclerosis, however, is often associated with occlusion in the intracranial branch vessels, such as the stems of the middle cerebral artery and the anterior cerebral artery without including the internal carotid arteries (25). The extent of the collateral vessels is restricted in these cases. The degree of proliferation of basal moyamoya vessels may therefore be associated with hemorrhagic risk. In addition, the anterior choroidal and posterior communicating arteries are hemodynamically overloaded with occlusion at the terminal portion of the internal carotid artery. Dilatation of the anterior choroidal and posterior communicating arteries is also reported to be a predictor of hemorrhage in adult moyamoya disease (26). Furthermore, moyamoya vessels develop for decades, beginning in childhood, in adult moyamoya disease. The vulnerability of the moyamoya vessels may increase with the passage of time (5).

The present study has several limitations. First, in this small cohort, multivariate analysis was not definitive. CMBs were not associated with known risk factors such as aging and hypertension in the present study, perhaps because of the small number of patients and the fact that most of them had these risk factors. Second, because the present study was cross-sectional, the risk for subsequent cerebral hemorrhage was not clear in patients with moyamoya-like vessels. Prospective data on clinical outcomes for patients with moyamoya-like vessels secondary to atherosclerosis are needed.

Conclusion

The prevalence and site of CMBs did not differ between patients with and without moyamoya-like vessels. Patients with moyamoya-like vessels secondary to atherosclerosis had a high frequency of ischemic cerebrovascular diseases, and slight symptomatic cerebral hemorrhage. Patients with moyamoya-like vessels secondary to atherosclerosis may not have a high risk of cerebral hemorrhage.

The authors state that they have no Conflict of Interest (COI).

Grant support: A grant from the Research Committee on Moyamoya Disease established by the Ministry of Health, Labor and Welfare of Japan

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D 脳血流測定
——2 SPECT，PET

Point

1 SPECT，PET診断の最大の利点は，放射性薬剤(トレーサー)の分布画像から脳血流量などの組織機能を表す示標が定量的な画像として得られるところにある．
2 脳血流SPECTトレーサーは，^{133}Xeなどの拡散型トレーサーと^{123}I-IMP，^{99m}Tc-HMPAO，^{99m}Tc-ECDなどの蓄積型トレーサーとに分類される．
3 蓄積型トレーサーの脳組織における摂取と保持の機構がそれぞれ異なるため，それぞれのトレーサーの特徴をよく理解しておくことが必要である．
4 ^{123}I-IMPを用いた脳血流SPECTの定量法として，microsphere法とautoradiography(ARG)法とが臨床応用されている．
5 血行力学的脳虚血の定量的重症度(stage 0～II)は，脳血流SPECTの定量画像解析から得られる安静時脳血流量と脳循環予備能により定義され，stage II(安静時脳血流量が正常値の80％未満かつアセタゾラミド反応性が10％未満)がPETにおけるmisery perfusionに相当する．
6 脳血流SPECTの統計画像解析には，定位定性的解析法であるZ-score解析と定位定量的解析であるSEE解析が臨床応用されている．

単光子放出コンピュータ断層法(single photon emission computed tomography；SPECT)および陽電子放出断層法(positron emission tomography；PET)は，ともに放射性薬剤(トレーサー)を体内に投与して，その体内分布を体外から断層画像として取り出す核医学画像検査法である．前者では主として脳血流分布が画像化され，後者では脳血流量，脳血液量，脳酸素代謝量，脳糖代謝量，神経受容体などが定量的に画像化されるが，いずれも脳の機能的画像診断法として臨床応用されている．一般にPETは測定精度にすぐれているが，医用サイクロトロンや薬剤の自動合成装置などの高額な機器を必要とするため，脳卒中領域での臨床応用はそれほど普及していない．一方，簡便で安価なSPECTは，その汎用性の高さから国内に広く普及しており，機器の改良とすぐれた脳血流トレーサーの開発とにより，脳卒中領域では盛んに臨床応用されている．そこで，本稿では主として脳血流SPECTの検査手技の特徴およびその画像解析方法について解説する．

1 SPECTの原理

SPECTで用いられるトレーサーは，ほとんどが200 KeV以下の低エネルギーγ線を放出する^{99m}Tc(半減期：6時間)または^{123}I(半減期：13時間)で標識されている．トレーサーの体内分布を画像化するためには，投与後に体内から放射されるγ線を回転型γカメラなどにより被検者の体軸周囲の多方向から収集し，これを投影データとしてトレーサーの分布画像を再構成する．SPECT装置には，空間分解能を向上させるために，特定の方向からのみのγ線を検出するためのコリメータの装着が必要である．しかし，これによって感度の劣化が生じるため，脳領域で使われる最近のSPECT装置にはガントリー内に複数のγカメラとファンビーム型のコリメータが装着され，空間分解能の向上と感度の改善が図られている．SPECTの空間分解能はPETよりも劣るが，半値幅(full width at half maximum；FWHM)で8mm前後まで改善している．また，SPECTの定量性はPETには及ばないが，その主原因であるγ線の体内での散乱と吸収に対する補正方法が実用化されつつある．散乱補正法では測定されたエネルギーウインドーから散乱線の成分を推定する技術が，吸収補正法では体内におけるγ線の吸収分布をトランスミッションCTなどにより測定する技術がすでに開発されており，SPECTの定量性は今後一般臨床でも大幅に改善するものと考えられる．SPECT診断の最大の利点は，トレーサーの分布画像から脳血流量などの組織機能を表す示標が定量的な画像として得られるところにある[1,2]．

2 脳血流SPECTトレーサー

脳血流を評価するためのトレーサーは，その脳内

表1 蓄積型脳血流トレーサーの特徴

放射性医薬品	IMP	HMPAO	ECD
標識核種	^{123}I	^{99m}Tc	^{99m}Tc
剤形	標識ずみ注射液	標識キット	標識キット、注射液
投与量	111～222 MBq	370～740 MBq	370～740 MBq
化合物の安定性	◎	○	◎
1回循環での摂取率	◎	○	○
血液中への逆拡散	少ない	多い	中程度
取り込み量と血流量との直線性	◎	△	○
血液中から脳への入力	緩徐に続く	投与直後のみ	投与直後のみ
経時的分布の変化	みられる	ほとんどみられない	わずかにみられる
血液脳関門障害の影響	ある（再分布像）	時にみられる	受けやすい
定量法	microsphere 法 ARG 法	Patlak plot 法	Patlak plot 法 microsphere 法
balloon occlusion test への応用	○	◎	◎
アセタゾラミド負荷試験への応用	◎	△	○
緊急検査	困難	可能	可能

挙動から拡散型トレーサーと蓄積型トレーサーとに分けられる．拡散型トレーサーには，^{133}Xeに代表される不活性ガスが分類される．これらは投与中に血流によって脳組織に拡散(wash-in)し，投与後は血流によって脳組織から洗い出される(wash-out)性質があるため，その過程を連続測定することにより，脳血流量を定量的に測定することができる．一方，蓄積型トレーサーには，^{123}I-IMP，^{99m}Tc-HMPAO，^{99m}Tc-ECDなどがある(後述)．これらの化合物はいずれも脂溶性が高く，脳血流分布に応じて高率に脳組織に摂取(extraction)され，その後長時間脳内に保持(retention)される性質をもつ．このような性質は，微小塞栓粒子(microsphere)になぞらえ化学的マイクロスフェア(chemical microsphere)ともよばれている．蓄積型トレーサーの脳組織における摂取と保持の機構がそれぞれ異なるため，トレーサーの分布は常に同等の脳血流分布を示すとは限らない．したがって，臨床応用に際しては，**表1**に示すそれぞれのトレーサーの特徴をよく理解しておくことが必要である[3]．脳血管障害の領域では，主として脳梗塞などの脳虚血病態の診断に用いられる．

a ^{123}I-IMP(N-isopropyl-^{123}I-p-iodoamphetamine)

^{123}I-IMPは，静脈内投与後その大部分が一度肺に取り込まれ，その後速やかに動脈血中に送り出される．初回循環において脳組織に90%以上と高率に摂取され，局所脳血流に比例して分布する．脳の放射能は投与後20～30分でピークに達する．^{123}I-IMPの投与初期の分布画像は，局所の脳血流分布を示すが，投与後の時間経過とともに脳組織に摂取された^{123}I-IMPが徐々に洗い出される．しかし，その一方で，初回循環で肺が^{123}I-IMPのreservoir(貯蔵器官)となり，ここから徐々に放出される^{123}I-IMPが脳組織に摂取される結果，数時間を経て再分布が生じる．初期分布像における^{123}I-IMPの摂取量と実際の脳血流との間の直線性(lineality)は，他の^{99m}Tc標識脳血流トレーサーよりもすぐれており，脳循環予備能の評価を目的とするアセタゾラミド負荷などにより，局所脳血流の賦活が行われた際にも局所の血流変化を最もよく反映する．また，^{123}I-IMPでは，microsphere modelや2-compartment modelなどの数学的モデル解析が適応され，脳血流量が定量測定される．

b ^{99m}Tc-HMPAO (^{99m}Tc-d, l-hexamethyl-propyleneamine oxime)

^{99m}Tc-HMPAOは，血液脳関門を通過後，水溶性の化合物に変化し，脳組織内に留まる．静脈内投与後，初回循環での脳への摂取率は80%前後と考えられるが，静注後1～2分後には定常分布となる．こうした脳内挙動はballoon occlusion(Matas)testなどの，脳血流遮断試験時の脳虚血の評価に適した特徴といえる．しかしながら，脳組織内での水溶性化合物への変換過程が瞬時ではないため，未変化の脂溶性化合物が組織から血液中に逆拡散する．脳血流量が高い領域ほど逆拡散も大きくなるため，最終的に組織に留まった^{99m}Tc-HMPAOの分布は必ずしも脳血流分布に比例しない．この逆拡散を数学的に補正しようという試みがLassenらにより開発されている．また，血液脳関門の破綻した亜急性期の脳梗塞では，血中で代謝された水溶性の^{99m}Tc標識化合物の過剰集積(hyperfixation)がみられる場合があり，luxury perfusion(ぜいたく灌流；脳血流量は増加しているが，脳酸素代謝量が低下している灌流異常)が過大に評価される[4]．^{99m}Tc標識脳血流トレーサーはコールドキット化されており，^{99m}Tcジェネレータを用意しておけば緊急検査に対応できるなどの利点がある．また，^{99m}Tc標識脳血流トレーサーでは，Patlak plot法により脳血流量の定量測定が試みられ

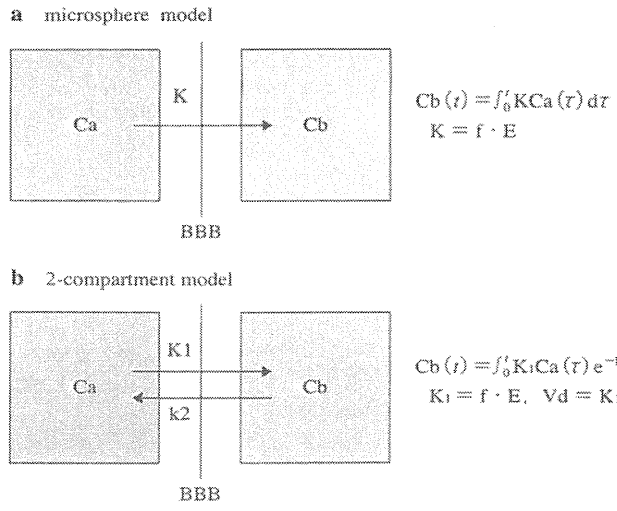

図1 蓄積型脳血流トレーサーを用いた脳血流の定量法（コンパートメント解析）
BBB：血液脳関門，K（K1）：トレーサーの血液から脳への移行速度定数，k2：トレーサーの脳から血液への移行速度定数（Vd=K1/k2：分布容積），f：局所脳血流量，Ca（t）：t時間後の血中放射能（入力関数），Cb（t）：t時間後の脳局所放射能，E：初回循環摂取率（$E=1-e^{PS/f}$〈PS：permeability-surface area product〉），

ている．

c ^{99m}Tc-ECD（^{99m}Tc-ethyl-cysteinate dimer）

^{99m}Tc-ECDは，^{99m}Tc-HMPAOとは異なる性質をもつ^{99m}Tc標識化合物である．初回循環での脳への摂取率は^{99m}Tc-HMPAOよりもやや低いとされるものの，脳組織から血液中への逆拡散の影響は少なく，血液中の放射能が速やかに消失するので^{99m}Tc-HMPAOよりも高画質のSPECT画像が得られる．^{99m}Tc-ECDの脳組織への保持機構は，脂溶性の^{99m}Tc-ECDが血液脳関門通過後，脳内の非特異的エステラーゼ活性による加水分解を受けて水溶性化合物に代謝され，脳実質内に保持されると考えられている．このような^{99m}Tc-ECDの保持機構は，脳梗塞などの病的脳組織で問題となる．亜急性期の脳梗塞巣では，血流の再開により豊富な血流が存在していても，^{99m}Tc-ECDの保持がみられない場合（hypofixation）[5]があり，luxury perfusionの評価が困難となる．^{99m}Tc-ECDの保持機構と脳組織viabilityとは密接に関連するため，亜急性期脳梗塞では，投与直後のdynamic SPECTと投与1時間後のstatic SPECTを用いることにより，前者でluxury perfusionの評価，後者で不可逆的組織障害の評価を行うことが可能である．

3 脳血流SPECT画像解析

a 定量画像解析法

蓄積型脳血流トレーサーでは，脳組織における各トレーサーの初回循環摂取率および保持機構の違いにより，各トレーサーの取り込み量と実際の脳血流量との間には理想的な直線性（lineality）は得られない．したがって，蓄積型脳血流トレーサーを用いた脳血流の定量測定では，各トレーサーの脳内挙動に応じた数学的モデルに，散乱・吸収補正後の実際のSPECT計数値と入力関数（動脈血中のトレーサー濃度曲線）を当てはめ，トレーサーの血液から脳組織への移行速度定数（K）を求め，Kと初回循環摂取率（E）から，局所脳血流量（f）をpixel by pixelに定量することが必要となる（コンパートメント解析，**図1**）．初回循環摂取率（E）については，E＝1.0として，局所脳血流の定量画像が得られている．蓄積型脳血流トレーサーのなかでは^{123}I-IMPの分布が真の血流分布に最も近く，モデル解析法が確立している．^{123}I-IMPを用いた脳血流SPECTの定量法として，microsphere法[6]とautoradiography（ARG）法[7]とが臨床応用されているが，ここではより簡便なIMP-ARG法とdual table ARG法について解説する．

1） IMP-ARG法

本法では，IMPの挙動を2-compartment model（組織からのトレーサーの洗い出しを考慮したモデル，**図1-b**）によって解析する．トレーサーの血液から脳への移行速度定数（K1）と，脳から血液への移行速度定数（k2）の比である分布容積（Vd = K1 / k2）を一定値（42 mL / mL）とし，個々の入力関数は，あらかじめ設定された標準入力関数を被検者の動脈血1点採血により較正し決定される．これにより，トレーサー投与後20～40分の間に撮像された1回のSPECT画像は，トレーサー投与後10分後に採血された動脈血から得られる入力関数によってpixel by pixelにK1画像＝脳血流（rCBF）定量画像へと変換される（IMPの初回循環摂取率を1.0とするとK1=rCBFとなる），アセタゾラミド負荷では，トレーサーの投与7分前に15～17 mg/kgを静注する．

2） dual table ARG法

IMP-ARG法では，安静時とアセタゾラミド負荷時脳血流量を別々の日に定量測定しなければならず，入力関数の測定誤差のために脳循環予備能を正確に評価できない場合がある．そこで，等量のト

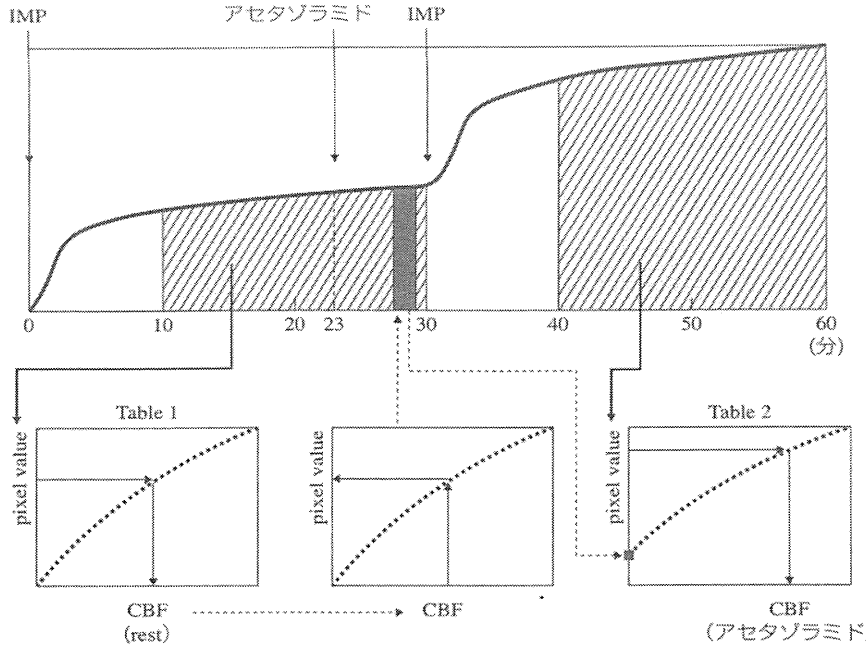

図2 dual table ARG 法

等量のトレーサーを用いて安静時とアセタゾラミド負荷時のSPECT計数値を連続的に求め，それぞれに対してSPECT計数値と脳血流量の関係を表すtableを作成することにより安静時とアセタゾラミド負荷時脳血流量の定量画像を得る方法である．安静時脳血流量の画像化では，IMP-ARG 法に準じて決定された入力関数を用いてSPECT計数値(左の斜線部分から得られるpixel value)と安静時脳血流量との関係がtable化され(左下のTable 1)，このtableを参照して各pixelの計数値が安静時脳血流量に変換される．アセタゾラミド負荷時血流量の画像化では，安静時と同一の入力関数を用いるが，各pixel での安静時終了時のSPECT計数値を起点として2回目のSPECT計数値(右の斜線部分から得られるpixel value)とアセタゾラミド負荷時脳血流量との関係がtable化され(右下のTable 2)，このtableを参照して各pixelの計数値がアセタゾラミド負荷時脳血流量に変換される．

(Kim KM, Watabe H, Hayashi T, *et al.* : Quantitative mapping of basal and vasoreactive cerebral blood flow using split-dose 123I-iodoamphetamine and single photon emission computed tomography. *Neuroimage* 2006 ; **33** : 1126-1135)

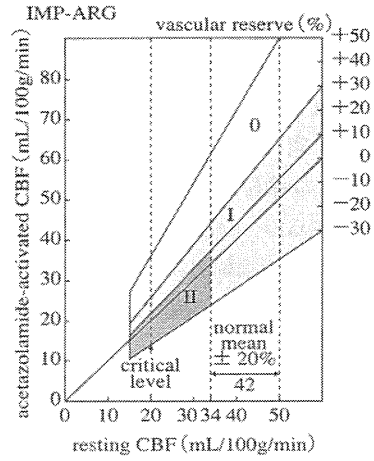

図3 安静時およびアセタゾラミド負荷時脳血流定量測定(^{123}I-IMP-ARG 法)による血行力学的脳虚血の定量的重症度評価(斜線の傾きが脳循環予備能の程度を示す)

stage 0：脳循環予備能：30% ≦

stage I：脳循環予備能：10% ≦，＜30%，
あるいは
脳循環予備能：＜10%，かつ
安静時脳血流量：≧正常値の80%

stage II：脳循環予備能：＜10%，かつ
安静時脳血流量：＜正常平均値の80%

レーサーを用いて安静時とアセタゾラミド負荷時のSPECT計数値を連続的に求め，それぞれに対してSPECT計数値と脳血流量の関係を表すtableを作成することにより安静時とアセタゾラミド負荷時脳血流量の定量画像を同時に得る方法が開発された(dual table ARG法，**図2**)．本法では，別日法で問題となる入力関数の測定誤差を排除するために，安静時1回の採血によって共通の入力関数を決定し，精度の高い安静時とアセタゾラミド負荷時脳血流量の定量画像をpixel by pixelに連続的に測定することができる．前述のIMP-ARG法とは異なり，トレーサーの脳内濃度が大きく変化する投与後10～30分間のデータが安静時のデータとして用いられるため，トレーサーの脳内濃度が安定する25～30分のデータで調整することにより測定精度の改善が図られる．

3) 血行力学的脳虚血の重症度評価

脳血流SPECTの定量解析に基づく血行力学的脳虚血の重症度評価では，安静時脳血流量とアセタゾ

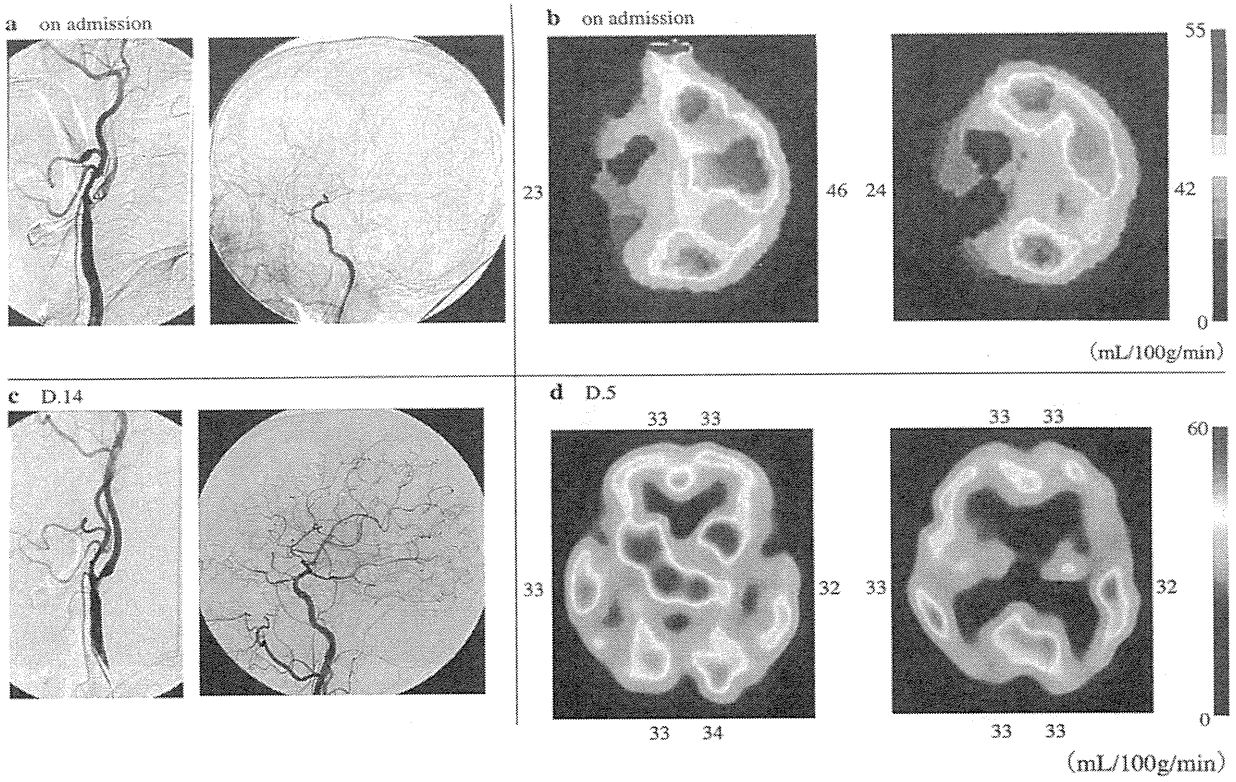

図4　急性期の進行性脳卒中例の脳血流 SPECT 定量画像解析

64歳，男性．徐々に増悪する左片麻痺にて発症．来院時の MRA にて右内頸動脈に狭窄が認められ，^{133}Xe-SPECT（**b**）では右中大脳動脈領域の脳血流量がクリティカルレベルまで低下していた．脳血管造影（**a**）では，右内頸動脈の狭窄部に浮遊している壁在血栓がみられ，末梢は描出されなかった．抗凝固および抗血小板薬等の薬物治療開始5日後の安静時脳血流 SPECT 定量画像解析（**d**）では右中大脳動脈領域の脳血流が正常化し，14日後の脳血管造影（**c**）では壁在血栓が消失し狭窄だけが残った．薬物治療によって劇的な改善が認められた症例であり，最終的には右内頸動脈狭窄に対して CEA が施行された．SPECT 画像の周囲の数値は，局所脳血流量を表している．

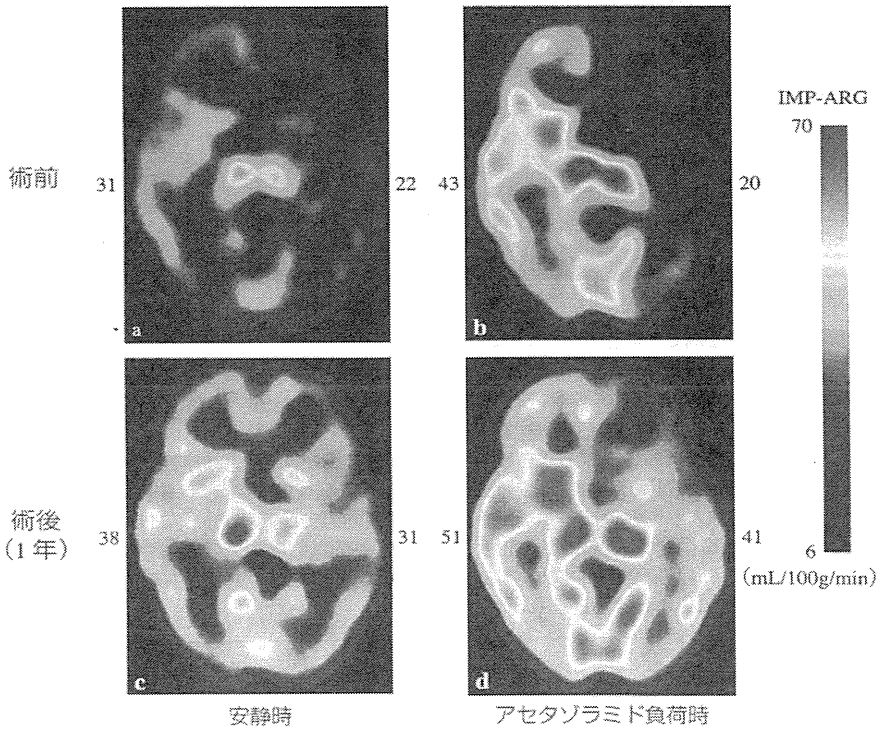

図5　慢性期の血行力学的脳虚血例の脳血流 SPECT 定量画像解析

65歳，男性．上段（**a**, **b**）：術前，下段（**c**, **d**）：術後1年．右片麻痺・言語障害にて発症した左内頸動脈閉塞症の慢性期の安静時脳血流 SPECT の定量解析（**a**）およびアセタゾラミド負荷時脳血流 SPECT の定量解析（**b**）を示す．図3の評価基準により，左中大脳動脈領域は血行力学的脳虚血 stage II と判定され，脳梗塞再発予防を目的とした EC-IC バイパス術の適応が決定された．術後1年の安静時脳血流 SPECT の定量解析（**c**）およびアセタゾラミド負荷時脳血流 SPECT の定量解析（**d**）では，左中大脳動脈領域は stage I と判定された．

ラミド負荷時脳血流量から，脳循環予備能［(アセタゾラミド負荷時脳血流量 / 安静時脳血流量 − 1) × 100%］を算出し，安静時脳血流量と脳循環予備能にそれぞれ閾値を設定して判定を行う．安静時およびアセタゾラミド負荷時の脳血流量を X-Y 座標軸上にプロットすると，血行力学的脳虚血の定量的重

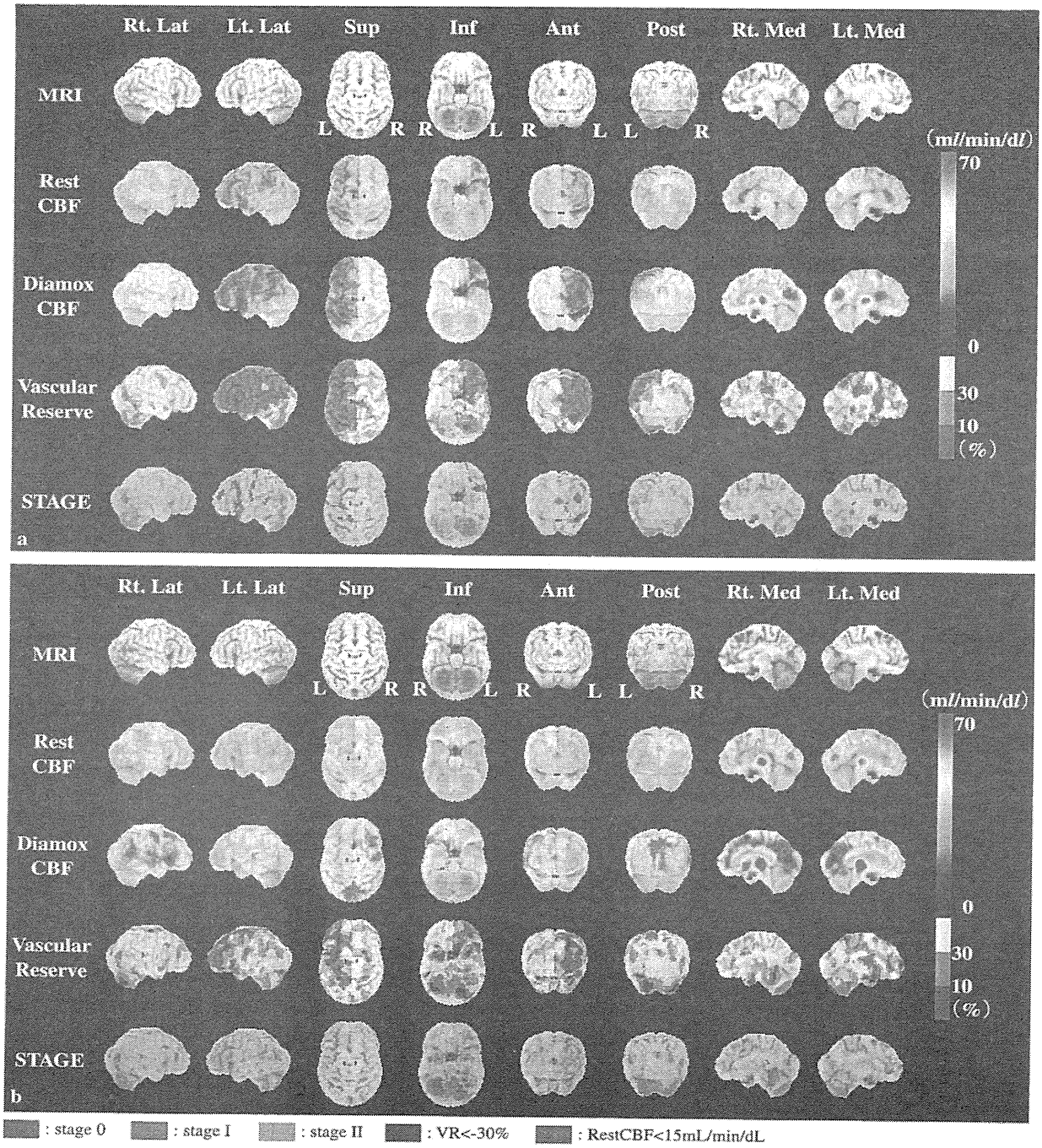

図6 図5の症例での脳血流SPECTのSEE解析

上段から，標準脳のMRI，安静時脳表血流量，アセタゾラミド負荷時脳表血流量，脳循環予備能，血行力学的脳虚血のstageであり，それぞれ右外側(Rt. Lat)，左外側(Lt. Lat)，上方(Sup)，下方(Inf)，前方(Ant)，後方(Post)，右内側(Rt. Med)，左内側(Lt. Med)の8方向からみた脳表画像を示す．

a：術前，左中大脳動脈領域および前大脳動脈領域内の一部に，安静時脳血流量の低下領域，アセタゾラミド負荷時の血管反応性の低下領域，脳循環予備能の低下領域，血行力学的脳虚血の重症度stage IIの領域がそれぞれ定位的に示される．

b：術後，左中大脳動脈領域および前大脳動脈領域内の安静時脳血流，アセタゾラミド負荷時の血管反応性，脳循環予備能などの各指標が術後いずれも改善し，血行力学的脳虚血の重症度も大部分の領域でstage 0～Iへと明らかに改善している．本法では，術前後における同一領内での各pixelにおけるstageの改善を定位的に判定できるとともに各stageの占める割合の変化をpixel数から算出し比較することも可能である．

症度(stage 0～II)は，**図3**のように階層性に定義され[8]，stage IIがPETにおけるmisery perfusion(貧困灌流：脳血流量〈cerebral blood flow；CBF〉は減少しているが，脳酸素代謝量〈cerebral metabolic rate of oxygen；$CMRO_2$〉が正常で，脳酸素摂取率〈oxygen extraction fraction；OEF〉が上昇している灌流異常)[9]に相当する．血行力学的脳虚血の定量的重症度評価は，急性期の進行性脳卒中における病態把握(**図4**)，慢性期の脳梗塞再発予防を目的とした脳血行再建術(EC-IC バイパス術)の適応決定(最終発作から3週間以上経過したのちに行った定量的脳循環測定にて，中大脳動脈領域の安静時脳血流量が正常値の

80%未満かつアセタゾラミド反応性が10%未満の脳循環予備能が障害された例に適応される．「脳卒中治療ガイドライン2009」)(**図5**)，頸部内頸動脈狭窄症に対する頸動脈内膜剥離術(carotid endarterectomy；CEA)のリスク評価，くも膜下出血後の脳血管攣縮による進行性脳虚血の評価などにおいて極めて有用性が高い．

b 統計画像解析法

脳血流SPECTの統計画像解析とは，被検者の脳血流SPECT画像にみられる脳血流の局所的な変動がはたして有意な変動であるかどうかを視覚的に判定するのではなく，正常群あるいは対照群の脳血流分布に関するデータベースと被検者(群)のデータをpixelごとに比較して有意な差を認める領域を統計学的に検証し，標準脳上に画像化する画像解析方法である．対照群と被検者(群)の各pixelにおけるデータは全脳または小脳などで正規化され，両者の差が対照群データベースの各pixelにおける標準偏差(SD)の倍数(Z-score)として標準脳上に画像化される(Z-score解析)．一般にZ-scoreが2以上と表示される領域については脳血流の変動が有意に大きいと判定される．統計画像解析の方法として，statistical parametric mapping(SPM)法や3-dimensional stereotactic surface projections(3D-SSP)法などが臨床応用されているが，ここでは3D-SSP画像の解析について解説する．

1) 3D-SSP法(Z-score解析)

本法では主として正常群の全脳表の血流分布に関するデータベースに対して，被検者の脳表血流分布の異常を精度よく検出することができる．定位脳座標系(Talairachの標準脳)に変換された正常群と被検者の脳表血流分布(全脳または小脳で正規化されたデータ)の差をpixelごとに正常群の標準偏差の値で除すことにより，被検者の全脳表のZ-scoreをpixelごとに算出し，その分布を通常8方向(右外側，左外側，上方，下方，前方，後方，右内側，左内側)からの三次元脳表画像として定位的に画像化する．Z-score解析は定位定性的な解析法であり，Z-scoreが大きな領域ほど，正常群に比べ血流の変動が大きい領域として定位的に表示される．脳表の血流(脳表から6 pixelの間で最大値)のみを用いるため，萎縮のある脳でも定位脳座標系への変換が容易であり，Alzheimer病などの認知症の早期鑑別診断における有用性がすでに報告されている．

2) stereotactic extraction estimation(SEE)解析

本解析法は，3D-SSP画像の脳座標系をプラットホームとして，脳血流SPECTを定位定量的に解析する方法として開発された[10]．本法では，安静時およびアセタゾラミド負荷脳血流量画像を3D-SSP画像の脳座標系に変換し，脳表の各pixelを定量値で表現する．次いで，各pixelについて血行力学的脳虚血の重症度を算出し，その分布を三次元脳表画像として定位的に画像化するとともに，あらかじめ指定された領域内のpixel数に対して各重症度のpixel数の割合を算出することもできる．**図6**は**図5**の症例の術前・術後における脳血流SPECT定量画像をそれぞれSEE解析した結果である．本解析法により，脳血流SPECTの定位定量的解析が可能となり，血行力学的脳虚血の定量的重症度評価の標準化が進むものと考えられる．

(中川原譲二)

Neurol Med Chir (Tokyo) 52, 245～266, 2012

Guidelines for Diagnosis and Treatment of Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis)

Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis; Health Labour Sciences Research Grant for Research on Measures for Intractable Diseases

CHAPTER I: CONCEPTS OF THE DISEASE

Concepts of the Disease

The characteristics of moyamoya disease (spontaneous occlusion of the circle of Willis, cerebrovascular "moyamoya" disease) on cerebral angiography were reported for the first time in 1957,[8] and the concept of moyamoya disease as a separate disease entity was established in the 1960s.[1-3,6,7] Pathologically, moyamoya disease is characterized by chronic progressive stenosis of the terminal portion of the bilateral internal carotid arteries, which leads to the formation of an abnormal vascular network composed of collateral pathways at the base of the brain (moyamoya vessels at the base of the brain) ('moyamoya' is the Japanese term for a "puff of smoke," which has been used to describe the appearance of these collateral vessels on cerebral angiograms[6]). Eventually, with bilateral internal carotid artery occlusion, the moyamoya vessels at the base of the brain derived from the internal carotid arteries disappear, and the entire brain is perfused by the external carotid artery system and the vertebrobasilar artery system.[1-3,5-7] This disease is included in the list of diseases for Research on Measures for Intractable Diseases and the Specified Disease Treatment Research Program specified by the Ministry of Health, Labour and Welfare. Currently, the diagnostic criteria for moyamoya disease (spontaneous occlusion of the circle of Willis) laid down by the research committee are as follows.[4]

Diagnostic Criteria[3]

(1) Cerebral angiography is considered essential for the diagnosis, and must show at least the following findings:
  (i) Stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or proximal portions of the anterior and/or the middle cerebral artery.
  (ii) Abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase.
  (iii) Bilaterality of findings (i) and (ii).

(2) However, when magnetic resonance imaging (MRI) and magnetic resonance angiographic (MRA) findings meet all of the following criteria, cerebral angiography can be omitted. See the "Guidelines for Diagnostic Imaging by MRI and MRA."
  (i) MRA shows stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or proximal portions of the anterior and/or the middle cerebral artery.
  (ii) MRA shows abnormal vascular networks in the basal ganglia.
  Note: When 2 or more visible flow voids are present in the basal ganglia on MRI, at least unilaterally, they can be deemed as representing an abnormal vascular network.
  (iii) Bilaterality of findings (i) and (ii).

(3) Moyamoya disease is an illness of unknown etiology. The differential diagnosis of this disease includes similar cerebrovascular lesions associated with the following underlying diseases, which should, therefore, be excluded: (i) atherosclerosis, (ii) autoimmune disease, (iii) meningitis, (iv) brain tumors, (v) Down's syndrome, (vi) von Recklinghausen's disease, (vii) head injury, (viii) cerebrovascular lesions after head irradiation, and (ix) others.

(4) Pathological findings that can be used as references for the diagnosis
  (i) Thickening of the arterial intima, mainly in the terminal portion of the internal carotid arteries, and narrowing or blockage of the lumen caused by this change, usually bilateral. Occasionally, lipid deposits are also present in the thickened intima.
  (ii) Arteries such as the anterior, middle, and

posterior cerebral arteries forming the circle of Willis occasionally show varying degrees of stenosis or occlusion associated with fibrocellular thickening of the intima, waviness of the internal elastic lamina, and thinning of the media.

(iii) Numerous small vascular channels (perforating and anastomotic branches) can be seen around the circle of Willis.

(iv) Pia mater may also show reticular conglomerates of small vessels.

Diagnostic Assessment

Moyamoya disease should be classified as definitive or probable based on the above-mentioned items (1) to (4). When autopsy is performed in the absence of cerebral angiography, the condition should be diagnosed based on the criteria in item (4).

Definitive moyamoya disease: All criteria listed in (1) or (2) and in (3) should be met. In children, however, the criteria in item (1) or (2) (i) and (ii) on one side, and visible stenosis around the terminal portion of the internal carotid arteries on the other side are sufficient for a definitive diagnosis.

Probable moyamoya disease: All criteria are fulfilled except item (1) (iii) and/or item (2) (iii) among the criteria of (1) or (2) and (3).

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CHAPTER II: EPIDEMIOLOGY

Moyamoya disease (spontaneous occlusion of the circle of Willis) is a disease that occurs frequently in Asian countries, including Japan, but is rare in Western countries. Epidemiological data reported from Japan are extremely valuable worldwide.

Early epidemiological surveys in Japan include an evaluation in 376 patients performed by Kudo[5] in the early 1970s and an evaluation in 518 patients conducted by Mizukawa et al.[6] Thereafter, a research committee on spontaneous occlusion of the circle of Willis was established in 1977. Since 1983, case registration and follow-up investigation have been carried out each year at medical institutions to which the committee members belong and their related facilities throughout Japan. As of 2006, there were a total of 962 patients, including 785 with a definitive diagnosis of moyamoya disease, 60 with a probable diagnosis, and 62 with quasi-moyamoya disease, registered in the database of this research committee on spontaneous occlusion of the circle of Willis.[7]

In addition to accumulation of cases in the database at the committee members' institutions, three large-scale national epidemiological surveys were conducted in 1984, 1990, and 1994.

Number of Patients and Male-to-Female Ratio

In a national epidemiological survey conducted by Wakai et al.[8] in 1994, approximately 3,900 people were estimated to be suffering from moyamoya disease (To be more precise, this was the number of patients examined). Moyamoya disease affects 3.16 people per 100,000 persons, and occurs at an incidence of 0.35 people per 100,000 population. According to the "number of patients having a certificate for medical care for specified (intractable) disease: Occlusive disease in circle of Willis," the number of patients with moyamoya disease markedly increased from 5,227 patients in 1994 to 10,812 patients in 2005. If a national survey were conducted again now, it is expected that the number of patients would have grown further from that in 1994. This may be attributable to the spreading awareness of and familiarity with the concepts of

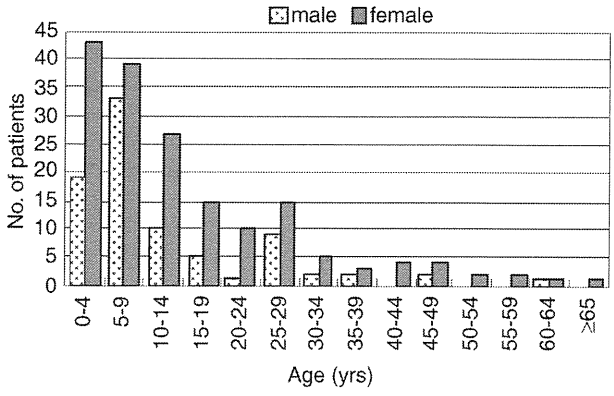

Fig. 1 Age of onset by sex.[7]

moyamoya disease, as well as the establishment of the "Guidelines for Diagnostic Imaging by MRI and MRA" in 1995, which enabled the diagnosis of moyamoya disease based on only the MRA findings.

The male:female ratio reported from various studies is nearly consistent,[7,8] 1:1.8 to 1.9. The disease is more common in women. In addition, a positive family history has been reported in about 10.0% of the patients.[8]

Age of Onset

The 1994 national survey[8] and 2006 database evaluation[7] showed a similar trend in relation to the age at onset of moyamoya disease: a bimodal peak consisting of a major peak in the first decade of life and a moderate peak in the late 20s to 30s (Fig. 1). However, a recent report has indicated a higher age as compared with that mentioned above as the peak age at onset.[1]

The various disease types by which the initial attack can manifest are presented in detail in Chapter IV: Symptoms. The 2006 database evaluation[7] has reported a unimodal peak age at onset in the late 20s for initial attacks of the hemorrhagic type, but a bimodal peak for initial attacks of other disease types (Fig. 2). However, according to another report, the peak age range of onset for initial attacks of the hemorrhagic type is the 5th to 6th decades of life (Chapter IV, Fig. 3).

Asymptomatic Moyamoya Disease

In recent years, asymptomatic cases of moyamoya disease and moyamoya disease manifesting with only non-specific symptoms, such as headache, have drawn attention. The increase in the number of such patients could be attributable, at least in part, to the current widespread availability of MRI and the increase in the number of people undergoing medical checkup procedures for the brain.

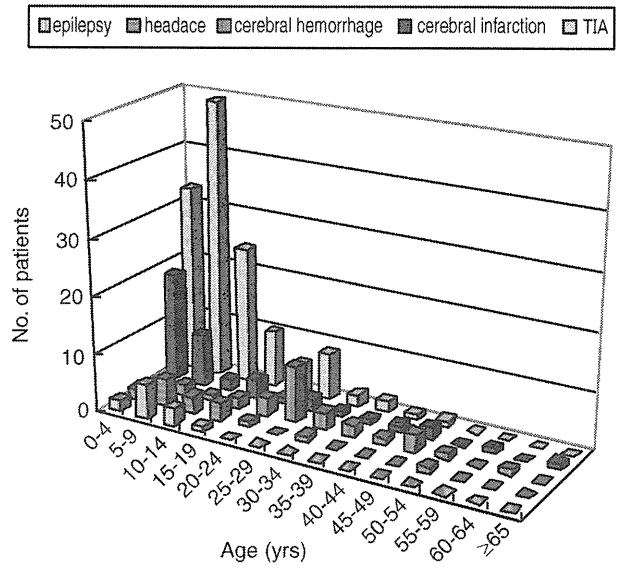

Fig. 2 Age of onset by disease type of the initial attack.[7] TIA: transient ischemic attack.

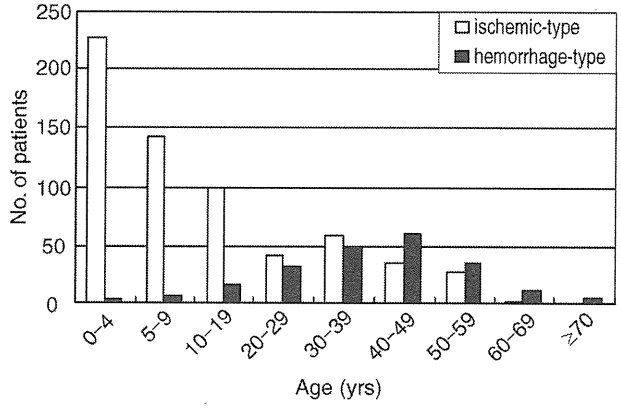

Fig. 3 Age of onset of ischemic-type and hemorrhagic-type moyamoya disease (n = 1127).

Ikeda et al.[3] performed MRI/MRA in 11,402 healthy people (male n = 7,570, female n = 3,832) who underwent a medical checkup for the brain and estimated a prevalence rate for moyamoya disease of 50.7 people per 100,000 healthy (asymptomatic) population. In an epidemiological survey conducted by Baba et al. in Hokkaido,[1] the prevalence rate of moyamoya disease was estimated as 10.5 people per 100,000 persons. This prevalence rate is higher than that reported from the previous national survey. While the possibility of including patients with atherosclerosis cannot be ruled out, it could include a considerable number of patients with latent

moyamoya disease (asymptomatic or only minor symptoms).

Distribution of Moyamoya Disease in the World

Goto and Yonekawa[2] reviewed papers published between 1972 to 1989 and reported that 1,063 patients had been notified as being affected by moyamoya disease in the world excluding Japan, and that of these, 625 patients were Asian (Korean n = 289, Chinese n = 245), 201 were European, and 176 were South or North American. The 1990 national survey reported an estimated 3,000 Japanese patients. Even allowing for differences in the rate of recognition of the disease, moyamoya disease appears to be a common illness in Asia, with the maximum number of cases from Japan. What is of even greater interest is that many patients of moyamoya disease reported from Europe and South/North America are Asian or African people, with the disease only rarely reported in Caucasians. Ikezaki et al.[4] also reported 451 patients from 29 institutions in South Korea in a 1995 survey.

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CHAPTER III: PATHOLOGY/ETIOLOGY

Pathology

The main finding at autopsy is stenosis or occlusion of the terminal portion of the internal carotid arteries. Moyamoya vessels are assumed to represent collateral circulation which has developed to compensate for the cerebral ischemia occurring due to stenosis. In the early stage of the disease (stage I according to Suzuki's classification), moyamoya vessels are rarely observed. Degeneration of the smooth muscle cells in the media and the resultant death of the vascular smooth muscle cells cause thinning of the media. The waviness and duplication of the internal elastic lamina, accumulation of necrotic cell components in the interstitium, and proliferation of the vascular smooth muscle cells induce thickening of the intima and narrowing of the intravascular lumen. These are the processes assumed to be involved in the formation of the occlusive lesions.[7]

These changes noted in the terminal portion of the internal carotid arteries suggest the possibility of similar occurrence in the systemic arteries.[11] Qualitative abnormalities of the vascular smooth muscle cells are considered to be an underlying reason for the internal carotid artery occlusion. Transcription factors such as tumor growth factor-β and growth factors such as basic fibroblast growth factor and human growth factor have also been implicated.[10]

Genetic factors are also considered to be closely involved; however, because penetrance is incomplete and depends on the age, accumulation of the effects of genetic factors is believed to induce vascular smooth muscle cell death and proliferation.[9]

Familial Moyamoya Disease

Both familial moyamoya disease, referring to the accumulation of affected patients among relatives, and sporadic moyamoya disease, where no affected per-