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Factors causing prolonged hypoperfusion after transient ischemic attack

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Even during the symptom-free stages, patients with a TIA often experience cerebral blood flow disturbances. In order to evaluate the factors which cause this abnormality, we studied the cerebral blood flow disturbance, anatomy and clinical status in 21 patients after TIAs. The results of ^{99m}Tc-hexamethyl-propylene-amine oxime SPECT were compared with CT, cerebral angiogram, cerebrovascular risk factors and clinical findings to determine which factor is most responsible for the hypoperfusion of brain after TIA. The overall sensitivity rates in detecting a lesion were 67% in SPECT and 19% in CT. The hypoperfused area tended to be large in patients who had intracranial, severe stenotic, multiple, or hemodynamically significant arterial lesions on the ipsilateral side. No such relationships were found between other examinations. We conclude that hypoperfusion after TIA essentially reflects a continuous cerebral blood flow disturbance that can be attributed to atherosclerosis of the cerebral arteries, with subsequent embolic and/or hemodynamic cerebral ischemia, although there may be a variety of processes.

Key words: TIA, cerebral blood flow, cerebral angiography, ^{99m}Tc-HM-PAO SPECT

INTRODUCTION

SEVERAL STUDIES of regional cerebral blood flow (rCBF) or CBF-single photon computed tomography (SPECT) have been performed in order to clarify the pathophysiology of transient ischemic attack (TIA),[1-7] because TIA presents a brief focal neurologic deficit and occurs as a prelude to ischemic stroke in as few as 20% and as many as 80% of cases.[8] However, previous studies of CBF after TIA have produced disparate results; normal rCBF,[1,2] decreased rCBF[3-5] or hyperperfusion with ischemia[6] have been reported. More recently, using ^{99m}Tc-hexamethyl-propylene-amine oxime (HM-PAO) SPECT, Bogousslavsky et al.[7] found a high incidence of early stroke in patients who had prolonged hypoperfusion after TIA. Thus, it remains to delineate in further studies the mechanisms underlying the prolonged hypoperfusion after TIA.

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We now report the results of ^{99m}Tc-HM-PAO SPECT in patients after TIAs. The results from CBF-SPECT were compared with computed tomography (CT), cerebral angiogram, cerebrovascular risk factors, and clinical parameters in an attempt to identify which factor is most responsible for the prolonged hypoperfusion after TIA.

PATIENTS AND METHODS

Patients

Twenty-one patients admitted to Osaka National Hospital, Osaka, Japan between 1989 and 1990 had a TIA. TIAs were defined according to the classification of the National Institute of Neurological Disorders and Stroke.[9] The mean age of the patients was 57.2±12.1 (±SD) years (range, 32 to 75 years). Thirteen were male and 8 females. The project was reviewed and approved by the Committee on Studies Involving Human Beings of the Osaka National Hospital. Informed consent was obtained in each case.

Clinical

A complete clinical history was recorded and a

neurologic examination was performed for each patient at the time of selection by the same neurologist. The neurologic deficits during the attack were classified in terms of physical signs: (I) motor dysfunction, (II) loss of vision, (III) sensory symptoms, (IV) aphasia, and (V) combination of symptoms I–IV.

CBF-SPECT

We used ^{99m}Tc-HM-PAO to assess the hypoperfusion of the brain. ^{99m}Tc-HM-PAO was prepared from a freeze-dried kit containing 0.5 mg of HM-PAO, 7.6 μg of stannous chloride, and 4.5 mg of sodium chloride in a vial (Amersham Medical Ltd., Tokyo, Japan). ^{99m}Tc-HM-PAO was reconstituted with 740 MBq (20 mCi) of ^{99m}Tc-sodium pertechnetate in 5 m*l* of solution at least 10 min before injecting the tracer via a 21-gauge cannula filled in with saline and free of blood into an antecubital vein. Image acquisition was started 5 min post injection. SPECT scanning was performed with a single-head rotating gamma camera fitted with a low-energy, high-resolution parallel-hole collimator and linked to a computer system (Toshiba GCA 901A). Sixty four views, 30 s frames collected over 360°, were recorded into a 128×128 matrix format, with the subject's head immobilized. Transaxial slices were reconstructed from the prefiltered raw data (9-point weighted filter) with the aid of filtered backprojection algorisms using a ramp filter. Sorenson's technique[10] (μ=0.12 cm^{-1}) was used for attenuation collection. No scatter correction was performed. Transaxial sections at 2.7 mm intervals were used for reconstructing 8.1 mm-thick computed images in planes parallel to the orbitomeatal line (OML). The resolution of this imaging system was measured as 19 mm full width at half-maximum (FWHM) in the plane of the reconstructed transverse sections.

We analyzed the SPECT images without correction of the HM-PAO back diffusion.[11] The CBF images of the clinically responsible cerebral hemisphere were reviewed by independent observers and classified with respect to the spatial extent or the location of the hypoperfused areas. The slices which had the largest hypoperfused area were used for analysis. The severity of hypoperfusion was graded as follows: (I) normal, (II) mild abnormality, generally less than 2.0 cm in the largest diameter, (III) discrete area of hypoperfusion larger than 2.0 cm involving less than one lobe, and (IV) multilobe involvement (Fig. 1). The location was classified into three groups: (I) no hypoperfused area, (II) subcortical lesion, and (III) cortical lesion. Discrepancies in SPECT ratings between observers were resolved by consensus. The mean interval from the last attack to SPECT was 25.6±13.3 days (range, 6–52 days).

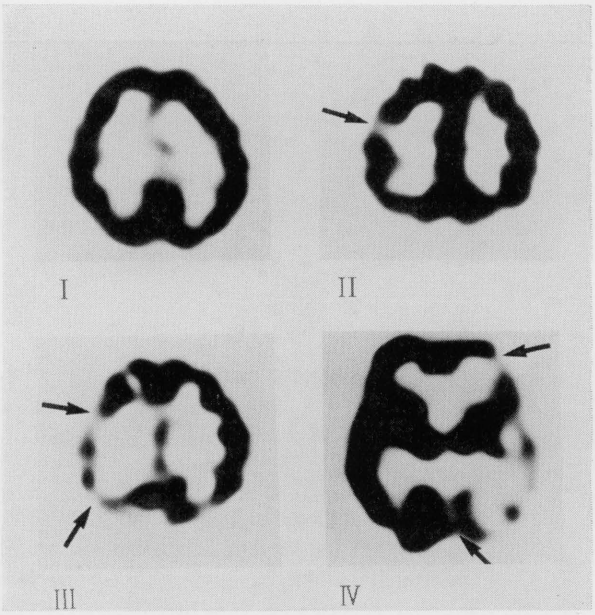

Fig. 1 An example of each SPECT class. SPECT images showing no hypoperfusion (I), showing a hypoperfused area with a maximum diameter less than 2.0 cm. (II), showing hypoperfused area larger than 2.0 cm involving less than one lobe (III), and showing hypoperfusion with multilobe involvement (IV). Hypoperfused areas are indicated by arrows. The images are displayed with a grey scale from 15% to 100% of the maximum counts.

CT

Conventional x-ray CT's of 1-cm layers between contiguous slices of the head without contrast enhancement were taken throughout the entire brain in planes parallel to the OML. The CTs were graded according to the presence (group II) or absence (group I) of the hypodense area. In all patients, CT preceded SPECT.

Cerebral Angiography

All patients underwent cerebral angiography. Intraarterial digital subtraction angiography (IA-DSA)[12] was performed in 18 patients less than 70 years old, and the remaining three, 70 years old or more, received intravenous (IV)-DSA. The cerebral angiograms were reviewed by a neuroradiologist who had no knowledge of the SPECT findings. The severity of angiographic abnormalities was categorized with respect to percentage stenosis, location, multiplicity and hemodynamic significance. All measurements were made directly on the radiographs. The percentage stenosis for each patient was calculated by measuring the luminal diameter at the narrowest point and dividing it by the normal luminal diameter of the vessel below the site of the stenosis. If no nar-

rowing of the vessel was observed, it was called a 0% stenosis and occlusion of the vessel was a 100% stenosis. The percentage of stenosis was classified into following groups: (I) no stenosis, (II) <25%, (III) ≥25% and <50%, (IV) ≥50% and <75%, and (V) ≥75%.

The location of the vascular lesions was classified into the following four groups: (I) no lesion, (II) extracranial, (III) intracranial, and (IV) extracranial plus intracranial.

The multiplicity of the lesions was classified into the three groups: (I) no vascular lesion, (II) solitary, and (III) multiple.

Evidence of a hemodynamically significant stenosis[13,14] was determined by the delayed filling of the middle cerebral artery branches relative to the external carotid branches (carotid), the prolonged cross-filling through the anterior circle of Willis (Willis), the arterial supply through the ipsilateral ophthalmic artery from the external carotid artery (ophthalmic), or the arterial supply through anastomotic channels across the surface from the anterior cerebral circulation (meningeal). The patients were classified into three groups: (I) no vascular lesion, (II) hemodynamically insignificant lesion, and (III) hemodynamically significant lesion.

Cerebrovascular risk factors and other parameters

The data included the following 12 information items:

Risk factors. Age, sex, blood pressure measured by indirect auscultation on admission, current or former cigarette smoking, fasting blood glucose concentration and cholesterol concentration the day after admission, and venous hematocrit on admission.

Cardiac investigations. Left ventricular hypertrophy (LVH), atrial fibrillation (AF), ischemic change in electrocardiography (ST) and two dimensional echocardiography (2DE).

Other parameters. End tidal CO_2 concentration ($P_{ET}CO_2$) during the SPECT.

Statistical analysis

Comparisons of the ordinal ranks of each data item were done by the Kruskal-Wallis and Mann-Whitney U tests.

RESULTS

Clinical features

Fourteen patients (66%) suffered from motor dysfunction; the neurologic deficits in the other patients were a loss of vision in three (14%), aphasia in one (5%), sensory symptoms in one (5%), and sensorimotor deficit in two (5%).

The mean number of TIA episodes before the study was 3.2±2.6; six patients (29%) experienced only a single episode of TIA, 12 (57%) two to five episodes, and three (14%) more than five episodes.

The mean duration of TIA was less than 5 min in 15 patients (71%), less than 30 min in four (19%), less than 5 hr in one (5%), and less than 8 hr in one (5%).

Hypoperfused area was found on the symptomatic hemisphere in 14 patients (67%); seven patients (33%) were categorized as group I, eight (38%) as group II, and six (29%) as group III. The hypoperfused area was most often located in the lenticular-capsular region (8 patients), followed in order of frequency by the parietal cortex (5), temporal cortex (3), and frontal cortex or occipital cortex (1) (Table 1).

The sensitivity of CT in detecting a lesion was lower than that of SPECT (19% versus 67%). The infarct was seen on CT in four patients (19%); internal capsule in two, and corona radiata or basal ganglia in one with the largest diameter less than 2.0 cm. Two patients had a hypodense area corresponding to the hypoperfusion on SPECT (Fig. 2). In cardiac investigation, LVH was found in three patients (14%), and ischemic change in one (5%). No patient had AF or abnormality in 2DE.

Fifteen patients (71%) showed signs of a stenotic

Table 1 Comparison of the location of the hypoperfused area with cerebral angiography

Cerebral angiography		Location of the hypoperfused area		
Severity of stenosis		N	S	C[b]
no lesion	I	3	3	0
<25%	II	4	3	0
≥25%<50%	III	0	2	1
≥50%<75%	IV	0	0	2
>75%	V	0	0	3
Location		N	S	C[b]
no lesion	I	3	3	0
extra	II	3	5	0
intra	III	1	0	4
extra and intra	IV	0	0	2
Multiplicity		N	S	C[a]
no lesion	I	3	3	0
solitary	II	4	5	3
multiple	III	0	0	3
Hemodynamic significance		N	S	C[a]
no lesion	I	3	3	0
no	II	4	5	2
yes	III	0	0	4

N=no hypoperfused area; S=subcortical; C=cortical. [a]$p<0.05$ and [b]$p<0.01$ compared with groups N and S.

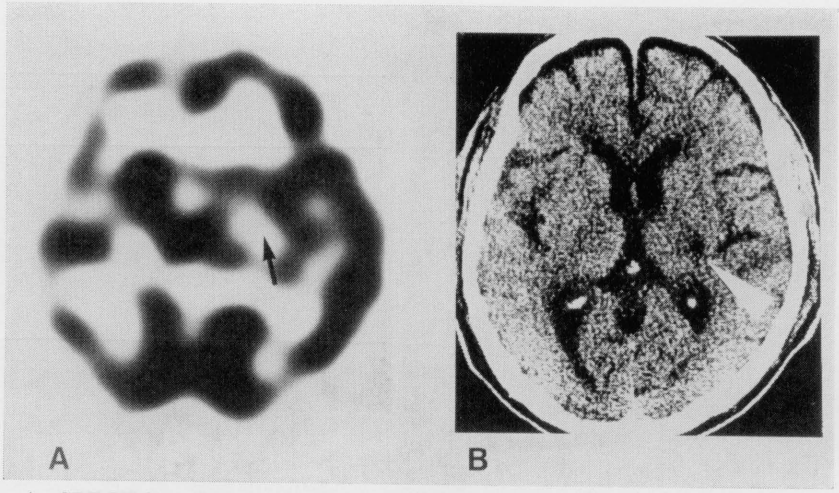

Fig. 2 A: SPECT in a 78-year-old male 37 days after a transient symptom of right hemiparesis showing a hypoperfused area in the left lenticular-capsular region (indicated by black arrow). (B): Computed tomogram (CT) at the same level showing a small hypodense lesion in the posterior genu of the left internal capsule (indicated by white arrow head).

Table 2 Comparison of SPECT with cerebral angiography

Cerebral angiography		SPECT			
Severity of stenosis		I	II	III[ab]	IV[bc]
no lesion	I	3	3	0	0
<25%	II	4	3	0	0
≥25%<50%	III	0	2	1	0
≥50%<75%	IV	0	0	1	1
>75%	V	0	0	2	1
Location		I	II	III[ad]	IV[ac]
no lesion	I	3	3	0	0
extra	II	3	5	0	0
intra	III	1	0	3	1
intra and extra	IV	0	0	1	1
Multiplicity		I	II	III	IV[ac]
no lesion	I	3	3	0	0
solitary	II	4	5	3	0
multiple	III	0	0	1	2
Hemodynamic Significance		I	II	III[ac]	IV[ac]
no lesion	I	3	3	0	0
no	II	4	5	2	0
yes	III	0	0	2	2

[a]$p<0.05$ and [b]$p<0.01$ compared with group I.
[c]$p<0.05$ and [d]$p<0.01$ compared with group II.
extra=extracranial; intra=intracranial.

lesion on angiography; extracranial arterial lesions were found in eight patients (38%), intracranial lesions in five (24%) and intracranial plus extracranial lesions in two (9%). The degree of stenosis was of group I in six patients (29%), group II in seven (33%), group III in three (14%), group IV in two (10%) and group V in three (14%). Four patients (19%) had a hemodynamically significant stenosis; collateral supply through the Willis was found in two patients, and through the carotid in two (Table 2).

Comparison of SPECT with other examinations

The SPECT class was not related to the classification of the neurological symptoms, delay between last attack and the examination, mean duration of attacks, the number of attacks, cerebrovascular risk factors, cardiac investigations, $P_{ET}CO_2$, or the CT class (Table 3).

Overall, the SPECT class and classification of the angiography were highly related (Tables 2, 3). The severity rating of the SPECT tended to be high in patients who had severe stenotic lesions ($\chi^2=12.8$; $p<0.005$), intracranial arterial lesions ($\chi^2=12.4$; $p<0.01$), hemodynamically significant stenosis ($\chi^2=10.1$; $p<0.05$), or multiple vascular lesions on the ipsilateral side ($\chi^2=9.0$; $p<0.05$). The hypoperfused area in the cortical territories was more extensive than that in the subcortical territories ($p<0.01$). Severely stenosed lesions ($\chi^2=12.8$; $p<0.005$), intracranial lesions ($\chi^2=12.3$; $p<0.005$), multiple lesions ($\chi^2=9.5$; $p<0.01$) in angiography were more frequently found in patients who had cortical hypoperfusion (Fig. 3) than those with a subcortical hypoperfusion (Table 1).

DISCUSSION

We found that, even during the symptom-free stages, hypoperfusion of the brain can be seen in about two-

Table 3 Comparison of SPECT with other variables

Variables	χ^2	p
Neurologic symptom	4.6	NS
Interval (day)	2.4	NS
Mean duration of TIA (min)	1.4	NS
Number of TIA	0.6	NS
MABP (mmHg)	4.7	NS
Men	3.6	NS
Total cholesterol (mg/dl)	2.9	NS
Hct (%)	2.7	NS
Smoking	2.3	NS
FBG (mg/dl)	1.7	NS
Age (yr)	1.4	NS
ST	1.6	NS
LVH	0.7	NS
$P_{ET}CO_2$ (mmHg)	0.9	NS
CT	1.6	NS
Stenosis	12.8	<0.005
Location	12.4	<0.01
Hemodynamic significance	10.1	<0.05
Multiplicity	9.0	<0.05

Interval=time interval between last TIA and examination; MABP=mean arterial blood pressure; FBG=fasting blood glucose concentration; Hct=hematocrit; LVH=left ventricular hypertrophy; ST=ST change in electrocardiography; $P_{ET}CO_2$=end tidal CO_2 concentration; Stenosis=degree of stenosis; Location=location of the stenotic lesions; Multiplicity=multiplicity of the stenotic lesions; NS=not significant.

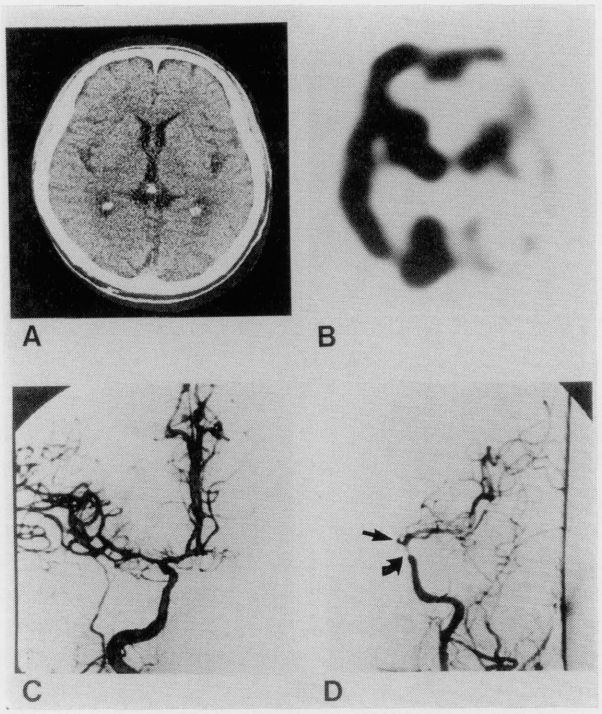

Fig. 3 A: CT in a 68-year-old male 10 days after a transient symptom of right hemiparesis showing no hypodense area. B: SPECT at the same level 14 days after TIA showed a prominent hypoperfused area in the frontal, parietal, temporal, and occipital cortices on the left hemisphere. C and D: Cerebral angiogram revealed severe stenosis (>90%) in the cavernous portion of the left internal cerebral artery (ICA) and occlusion of the left anterior cerebral artery (ACA) (indicated by arrows) (D). The blood flow in the left ACA was supplied from the contralateral ICA through the anterior communicating artery (C).

thirds of patients with TIAs, and that the extent of the hypoperfused area was related to the presence of the intracranial, multiple, severely stenotic, or hemodynamically stenotic lesions in the ipsilateral large-vessels.

TIA has been thought to be caused either by distal occlusion of cortical branches of the artery from embolic material originating in a carotid atherosclerosis, or by distal hemodynamic consequences resulting from reduced blood flow through the carotid with adequate collateral flow.[15] Furthermore, cardiac arrhythmias[16] and lacunar infarctions[17] are becoming increasingly recognized as conditions which can lead to symptoms identical to those of large-vessel atherosclerotic disease. From the viewpoint of CBF, the hypoperfused area of ischemic stroke may include infarcted tissue, regions with diaschisis,[18], with diffuse loss of small neurons with normal findings on CT[19] or with reduced cerebral perfusion pressure.[14] It is, therefore, important to clarify the pathogenesis of TIA in relation to the mechanisms for TIA onset, and the cerebral blood flow disturbance.

The hypoperfused area was most often located in the lenticular-capsular region in our study population; two out of eight patients showed a small hypodense area on CT which corresponded to the hypoperfused area on SPECT and was indicative of the symptoms. These patients, therefore, may be categorized as having cerebral infarction with transient signs (CITS)[20] and the hypoperfused area was considered to reflect infarcted tissue. Because of the low sensitivity of CT to detect small lacunar infarctions,[21] more lesions could be detected by means of magnetic resonance imaging in the other six patients. In addition to lacunar infarction caused by small-vessel occlusion,[17] emboli from an intra-arterial source[22] or a cardiac source[23] may cause cerebral ischemia in the subcortical territories. In previous studies, prevalence of carotid disease was found only in 5% of asymptomatic patients over the age of 60 years,[24] and 31% of patients with lacunar infarction.[25] We found carotid stenosis in five out of eight (63%) patients with a hypoperfused area in the lenticular-capsular region; the degree of stenosis was 0% in three patients, <25% in three, and 25–50% in two.

No intracranial or multiple lesions were observed. Furthermore, no patient had a past history of systemic hypotension, severe carotid artery stenosis, or abnormalities in the cardiac investigations. Thus, the higher incidence of abnormal carotid angiography in these patients may indicate that small-vessel obstruction as well as emboli from the large-vessel are major causes of the CBF disturbance.

In the group with a hypoperfused area in the cortex, all patients had an abnormal angiogram. In these patients, the severity rating of the vascular stenosis and hypoperfusion, and the incidence of the intracranial or multiple lesions were higher when compared to the lenticular-capsular group. As the size of the atherosclerotic plaque increases, it may reduce perfusion pressure or increase the risk of thromboembolism. Hypoperfused areas during the symptom-free stage of TIA may, therefore, reflect previous or continuing[6] cerebral tissue damage induced by hemodynamic or embolic mechanisms, or both, resulting from the atheromatous vessels. We found marked hypoperfusion in patients with evidence of a hemodynamically significant stenosis. The hypoperfused area in patients with severe (>60%) atherosclerotic plaque[26] may be further classified according to the cerebrovascular reserve capacity (CRC).[27] Hypoperfusion with normal CRC indicates that decreased metabolic demand is linked to decreased CBF due to the ischemic tissue damage (matched low-perfusion), and hypoperfusion with decreased CRC[27] indicates that compensatory vasodilation due to severe reduction in cerebral perfusion pressure (CPP) is insufficient to maintain CBF (misery perfusion; CBF reduction with increased oxygen extraction fraction). Powers et al.[14] reported that the primary determinant of cerebral perfusion pressure and CBF is the adequacy of collateral circulation pathways. If the cerebrovascular reserve capacity is measured in our patients, the cause of hypoperfusion may be more clearly defined. We believe that hypoperfusion in carotid TIA reveals either ischemic tissue damage with matched low-perfusion or a misery-perfusion state.

We postulate that the close relationship between the presence of intracranial vascular lesions and the extent of the hypoperfused area can be explained by a high incidence of severe atherosclerotic lesion in the intracranial portion of the internal carotid artery in Japanese,[28] while in Americans, severe lesions are located more often in the extracranial portion of the internal or common carotid arteries. Wecksler et al.[13] reported that most of the events in American patients with hemodynamically significant carotid siphon stenosis were TIAs or minor strokes. The prognosis of the carotid siphon stenosis should be evaluated in future with respect to racial differences.

The mechanisms causing TIAs in patients with normal results remain unclear. In spite of extensive testing, we found no abnormality in three patients. A small carotid ulcer may be missed by angiography,[29] and transient arrhythmias or cardiac abnormalities below the resolution of echocardiography could result in emboli.[30] Because of the delay between the onset of TIA and the tests any of the hypoperfused areas may have been restored to normal by the time of the test.

We conclude that hypoperfusion after TIA is a long-lasting, relatively fixed abnormality of the cerebral circulation, which is secondarily caused by atherosclerosis of the cerebral arteries, with subsequent embolic and/or hemodynamic cerebral ischemia. None of the hypoperfused areas can be considered as clinically insignificant because, in most patients after TIA, the hypoperfused area may reflect previous clinical and/or subclinical episodes[20] of cerebral ischemia.

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