Relationship between Cognitive Function and Regional Cerebral Blood Flow in Stroke Patients Using 99mTc-ECD SPECT 3DSRT

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ABSTRACT

The purpose of this study was to investigate the associations between regional cerebral blood flow (rCBF) and cognitive function in patients having a local stroke within the thalamus or putamen. The Mini-Mental State Examination (MMSE) and the Kohs Block Design Test (KBDT) were used to evaluate cognitive function. Brain single-photon emission computed tomography (SPECT) was performed with 99mTc-ethyl cysteinate dimer and analyzed with a 3-dimensional stereotactic region-of-interest template. Subjects were divided into subgroups according to the total MMSE score (D [Dementia : 23 points or less] and N [Normal : 24 points or more]) and according to KBDT scores (B [Bad : less than IQ 70] and G [Good : IQ 70 or more]). The rCBF was decreased in the MMSE D subgroup, especially in patients with a left putamen lesion, and in the KBDT B subgroup, especially in patients with a left thalamus lesion. When the lesion was in the right hemisphere, no significant difference in rCBF was found between the MMSE D and N subgroups or between the KBDT B and G subgroups. SPECT is useful for clinical evaluation of cerebral vascular disease, especially in patients with left hemispheric lesions. Additional data and further detailed evaluations are needed. (Jikeikai Med J 2006 ; 53 : 151-8)

Key words : single-photon emission computed tomography, cognitive function, Mini-Mental State Examination, Kohs Block Design Test, thalamus, putamen

INTRODUCTION

After cancer and heart disease, stroke is the leading cause of death in most developed countries, including Japan. It is also a major cause of morbidity, long-term disability, hospital admissions, and healthcare costs[1]. Stroke is often complicated by cognitive dysfunction. In cases of cognitive dysfunction, hospitalization is prolonged even though paralysis is slight, and return to home is often disrupted. To evaluate cognitive function in stroke patients, we have administered cognitive function tests and performed imaging studies to detect the lesion area affecting cognitive dysfunction. Recently, various methods have been developed for imaging of brain function, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). SPECT, which uses radiolabeled blood-flow tracers, such as a technetium-99m hexamethyl-propylene amine oxime, 99mTc ethyl cysteinate dimer (ECD) and 123I-iodoamphetamine, are useful for detecting acute ischemic stroke by demonstrating hypoperfusion earlier than does conventional

MRI. ^{99m}Tc-ECD SPECT is a good marker of regional cerebral blood flow (rCBF) and is useful for evaluating cellular viability even in cases of sufficient perfusion. Thus, we have been able to apply a common template of a region of interest (ROI) automatically according to variations in the shape of the brain by using a 3-dimensional stereotactic ROI template (3DSRT)[2,3] and more accurately measure rCBF than was previously possible.

The purpose of this study was to investigate the associations between rCBF and cognitive function in patients having a local stroke within the thalamus or putamen. However, it is not yet certain whether there is a relation between rCBF and results of cognitive evaluations, especially in stroke patients. The Mini-Mental State Examination (MMSE) and the Kohs Block Design Test (KBDT) are easy to perform and have been used worldwide for cognitive evaluation. For the purposes of this study, we performed brain SPECT using ^{99m}Tc-ECD and analysis by 3DSRT in patients with stroke. We also examined cognitive function in these subjects by means of the MMSE and KBDT. To our knowledge, no previous studies have examined the relationship between rCBF and results of the KBDT.

Subjects and Methods

All patients consecutively admitted to the Department of Rehabilitation Medicine, at Tokyo Metropolitan Otsuka Hospital, from December 2003 through May 2006 were included in this study if they met the following 5 criteria : 1) first stroke ; 2) lesion limited to the thalamus or putamen ; 3) no midline shift shown in imaging (computed tomography [CT] or MRI) ; 4) right handedness ; and 5) no surgical procedure performed.

We studied 73 stroke patients (53 men and 20 women ; age, 60 ± 10 years [mean$\pm$standard deviation]) Of these patients, 48 had cerebral hemorrhages and 25 cerebral infarctions, with 35 left hemispheric lesions and 38 right hemispheric lesions. The mean duration of disease was 72 ± 42 days (mean$\pm$standard deviation).

After admission to our hospital, all subjects underwent MRI or CT to ensure that there was only one hemispheric lesion within the thalamus or putamen and no brain atrophy or other anatomical disorders. We also administered the aphasic battery test to rule out the presence of aphasia. Patients with aphasia were excluded because the MMSE requires linguistic competence. All subjects gave informed consent in accordance with our Institutional Review Board guidelines. A signed consent form was obtained from each subject.

SPECT

SPECT was performed with a triple-head gamma camera (GCA9300A, Toshiba Medical Systems, Tokyo) fitted with a low-energy, super-high-resolution fan-beam collimator. Radionuclide angiography was performed immediately after intravenous bolus injection of 600 MBq of ^{99m}Tc-ECD over 2 minutes. Ten minutes later, consecutive SPECT imaging was performed for 11 minutes with the patient lying quietly in the supine position with eyes closed. Collections were performed with a 64×64 matrix. Attenuation corrections were performed with a 3.4-mm slice thickness in the coronal and sagittal planes. The obtained data were corrected with Lassen's correction (correction coefficient $\alpha = 2.59$). Scatter correction was done with the triple-energy window method.

We used a 3DSRT version 2 program to analyze SPECT data. This program can outline 12 segments including 318 ROIs per 59 slices automatically on one side. This program uses Statistical Parametric Mapping 99 only for anatomical standardization, and applies a common ROI template to each datum (Fig. 1). In this study we used 7 segments (both sides) of the cerebral hemisphere cortex (callosomarginal, precentral, central, parietal, temporal, angular, and posterior).

Evaluation of cognitive function

Cognitive function was assessed in all subjects with the MMSE and KBDT before and within 1 week after SPECT. We divided the subjects into 2 subgroups according to the MMSE total score : D (Dementia : 23 points or less) and N (Normal : 24 points or more) and into 2 additional subgroups
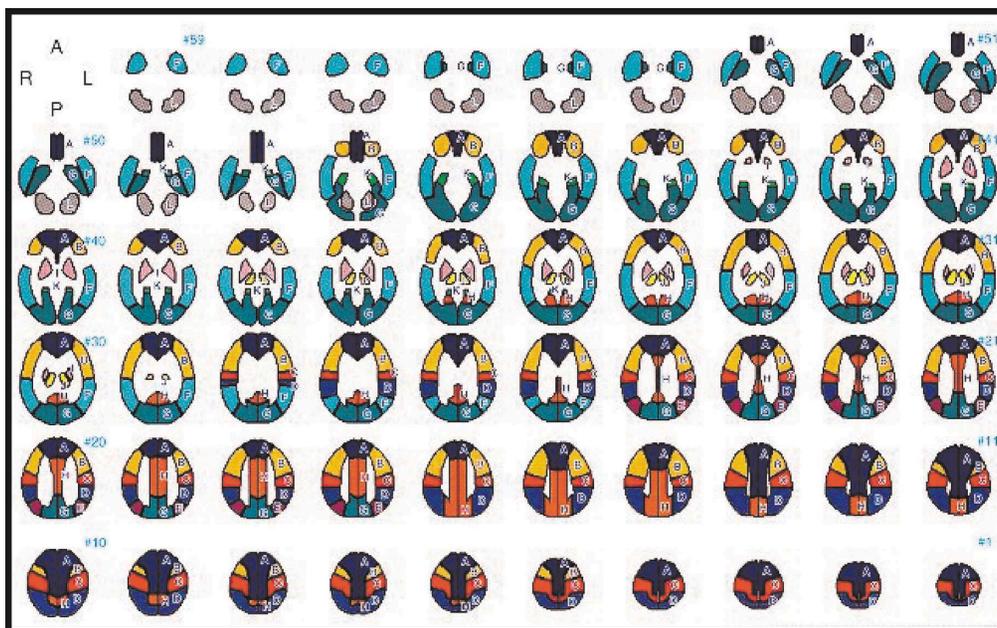
ROI No	Name	Slice	ROIs
A	callosomarginal	1-53	53
B	precentral	5-47	43
C	central	1-28	28
D	parietal	1-28	28
E	angular	17-24	8
F	temporal	25-59	35
G	posterior	17-56	40
H	pericallosal	6-36	31
I	lenticular nucleus	30-43	14
J	thalamus	29-38	10
K	hippocampus	35-49	15
L	cerebellum	47-59	13

Fig. 1.   The template of the 3DSRT version 2 program.   The 3DSRT version 2 program has the common ROI template.   Twelve segments are composed of 318 ROIs, which were present in 59 slices on one side.

according to Kohs IQ: B (Bad: less than IQ 70) and G (Good: IQ 70 or more).   We statistically compared the rCBF in 7 segments in each set of subgroups (D and N, and B and G) separately according to the lesion side.   We also compared rCBF in subgroups between lesion areas (putamen or thalamus).   Table 1 summarizes the data of study subjects according to their

groups.   There was no significant difference in age between patients with lesions on the right or left side in any subgroup.

Data Analysis

All data are expressed as means±standard deviation.   Comparisons were made by means of unpaired

Table 1.   Number and age of each subgroup

subgroups		lesion side	no. subjects (putamen, thalamus)	age (years)
MMSE				
≦23	D	left	18 (11, 7)	65±10
		right	12 (5, 7)	67±6
≧24	N	left	17 (10, 7)	57±9
		right	26 (23, 3)	57±11
Kohs IQ				
<70	B	left	16 (7, 9)	69±8
		right	15 (11, 4)	62±7
≧70	G	left	19 (14, 5)	55±7
		right	23 (17, 6)	58±12
lesion side		left	35 (21, 14)	62±10
		right	38 (28, 10)	59±10
total			73 (49, 24)	60±10

Table 2.   rCBF of each segment of subgroups D and N

	rCBF (mean±SD) ml/100 g/min					
	lesion side					
segment	right			left		
	D	N	p	D	N	p
Rt-callosomarginal	33±5	37±4	nd	35±3	41±5	**
Lt-callosomarginal	36±4	39±5	nd	34±3	40±5	**
Rt-precentral	31±5	35±5	nd	36±3	41±5	**
Lt-precentral	37±4	40±5	nd	33±3	39±5	**
Rt-central	32±5	34±4	nd	39±4	43±5	nd
Lt-central	40±4	41±5	nd	34±5	39±6	nd
Rt-parietal	34±5	36±4	nd	39±4	45±6	*
Lt-parietal	39±5	41±6	nd	34±5	40±6	*
Rt-angular	36±5	39±5	nd	41±4	47±7	*
Lt-angular	42±4	45±6	nd	38±4	44±7	*
Rt-temporal	30±5	35±6	nd	35±3	41±6	**
Lt-temporal	36±4	39±6	nd	31±3	37±6	**
Rt-posterior	40±5	44±6	nd	43±3	48±7	nd
Lt-posterior	43±5	46±6	nd	42±4	46±6	nd

Rt : right
Lt : left
D : subgroup D (MMSE total score ; 23 points or less)
N : subgroup N (MMSE total score ; 24 points or more)
p : unpaired Student's t-tests (**, $p<0.01$; *, $p<0.05$; nd, no significant difference)

Student's t-tests.   A p value less than 0.05 indicated a statistically significant difference.

RESULTS

Relationship between MMSE and rCBF

In subjects with a right hemispheric lesion, rCBF did not differ significantly between the D and N subgroups in any segment.   However, in subjects with a left hemispheric lesion, rCBF in the D subgroup was significantly lower than that in the N subgroup in the callosomarginal, precentral, parietal, angular, and temporal segments (Table 2).   When the damage was limited to the thalamus area, no difference in rCBF between the D and N subgroups was shown in any segment regardless of the lesion side.   However, when damage was limited to the putamen area, a significant difference in rCBF was found between the D and N subgroups in both left and right callosomarginal, precentral, and temporal segments and the left parietal and left angular segments (Fig. 2).   In patients with a right putamen lesion, there was no significant difference between subgroups in the rCBF in any segment.
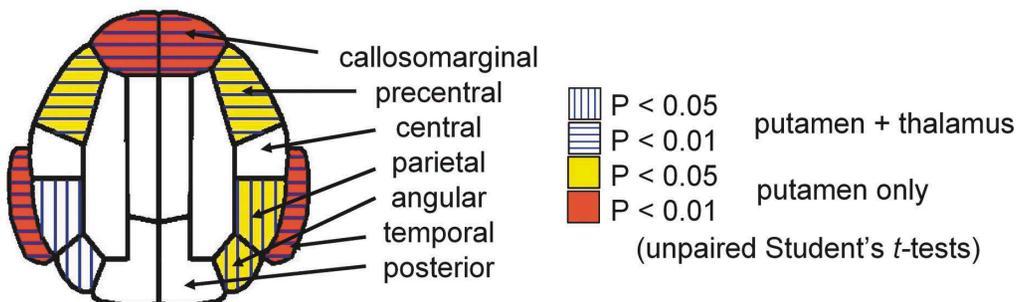

Fig. 2.   Segments with significant differences between the MMSE D and N subgroup in subjects with a left lesion (putamen+thalamus, putamen only).
D : subgroup D (MMSE total score : 23 points or less)
N : subgroup N (MMSE total score : 24 points or more)

Relationship between KBDT and rCBF

　　Table 3 shows rCBF in each segment according to lesion side.　The rCBF in the B subgroup was significantly lower than that in the G subgroup in both callosomarginal segments, both precentral segments, and the right parietal, right angular, and right temporal segments in subjects with left hemispheric lesions. In subjects with a right hemispheric lesion, differences in rCBF were not significant between the B and G subgroups in any segment.　When damage was limited to the putamen area, no difference in rCBF between the B and G subgroups was shown in any segment regardless of the lesion side.　However, in subjects with a left thalamus lesion, rCBF differences between the B and G subgroups were found in both the right and left callosomarginal and precentral segments and in the right central, parietal, angular, temporal, and posterior segments (Fig. 3).　When damage was limited to the right thalamus area, no significant differences in rCBF were noted between subgroups in any segment.

Table 3.　rCBF of each segment of subgroups B and G

segment	rCBF (mean±SD) ml/100 g/min					
	lesion side					
	right			left		
	B	G	p	B	G	p
Rt-callosomarginal	34±5	37±4	nd	35±4	41±5	**
Lt-callosomarginal	37±5	39±4	nd	34±4	39±5	*
Rt-precentral	32±5	35±5	nd	36±4	41±5	**
Lt-precentral	39±6	40±4	nd	34±3	38±5	*
Rt-central	32±5	34±4	nd	39±4	43±5	nd
Lt-central	41±5	41±4	nd	35±5	38±7	nd
Rt-parietal	34±4	36±4	nd	39±4	45±6	*
Lt-parietal	40±5	40±5	nd	35±4	39±7	nd
Rt-angular	36±5	39±4	nd	41±4	47±7	**
Lt-angular	44±6	44±5	nd	39±4	43±7	nd
Rt-temporal	31±4	35±6	nd	34±3	41±5	**
Lt-temporal	38±5	38±5	nd	32±3	36±7	nd
Rt-posterior	41±5	44±6	nd	43±3	48±6	nd
Lt-posterior	45±6	45±6	nd	42±4	46±6	nd

Rt : right
Lt : left
B : subgroup B (Kohs IQ ; less than 70)
G : subgroup G (Kohs IQ ; from 70 or more)
p : unpaired Student's t-tests　(**, $p<0.01$; *, $p<0.05$; nd, no significant difference)

DISCUSSION

MMSE

　　The MMSE is generally used as a screening examination of the whole brain for cognition.　Therefore, the widespread decrease in rCBF in subjects of the D subgroup with a left hemispheric lesion was appropriate.　Cerebral blood flow has been reported to decrease over a wide range of both hemispheres in vascular dementia[4].　However, in subjects with a right hemispheric lesion, we found no significant difference in rCBF in any segment between subgroups D and N.　We did not exclude subjects with minor hemispheric symptoms due to a right hemispheric lesion if they could complete the examination.　A minor hemispheric symptom, such as that involving attention, might have masked the relation between the MMSE score and rCBF in subjects with right hemispheric lesions.　Our findings indicate that the results of the MMSE cannot be predicted with rCBF in patients with a right hemispheric lesion.
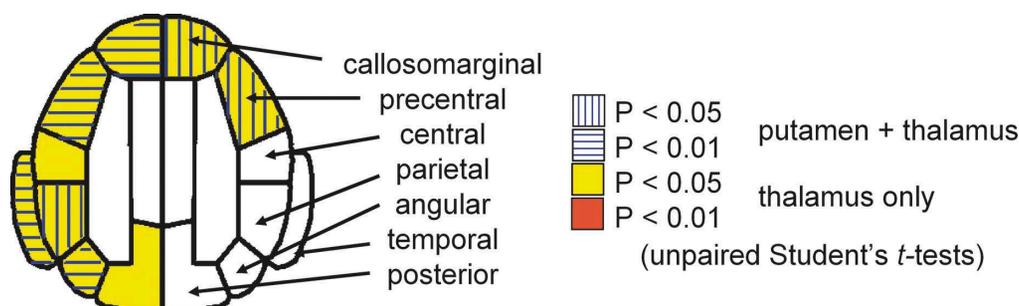

Fig. 3.　Segments with significant differences between Kohs IQ B and G subgroups in subjects with a left lesion (putamen+thalamus, thalamus only).
　　　　B : subgroup B (Kohs IQ : less than 70)
　　　　G : subgroup G (Kohs IQ : from 70 or more)

We found significant differences in rCBF between subgroups D and N in some segments in subjects with left putamen lesions but not in subjects with a left thalamus lesion, even though both lesions were on the left side. The MMSE requires linguistic competence, and the left putamen is nearer the speech center than is the left thalamus. We excluded patients with aphasia, as noted above, but language function may have still been impaired and influenced results.

Age is reported to be an important factor in MMSE results in healthy elderly persons[4,5], but the cognitive function differs fundamentally between the normal aging brain and a brain with hypoperfusion due to stroke. Hypoperfusion is slight in the normal aging atrophic brain[6].

KBDT

KBDT is a widely used evaluative tool, but to our knowledge the relationship between rCBF and KBDT has not been examined. The advantages of this test are that even a child can take it and language differences do not matter because it is nonverbal. Also, it is easily administered and not time-consuming. Whereas the MMSE evaluates the general cognitive function of the whole brain, KBDT evaluates higher-order functioning, especially performance IQ and constructional function, mainly in the right hemisphere. These are not independent functions ; in particular, unilateral spatial neglect obstructs the operation of this test[7]. A tendency toward low constructional function is present in patients with right hemispheric lesions[8], but the relation to cerebral blood flow is unclear. Our results showed right-biased hypoperfusion in subjects of the low Kohs IQ group with left hemispheric lesions. This finding suggests that Kohs IQ is affected by right hemispheric blood flow. However, in subjects with right hemispheric lesions, there was no significant difference in rCBF between the low and high Kohs IQ groups. We suggest that the right hemispheric lesion caused the nerve disconnection in the right hemisphere and that the constructional function was directly influenced by the nerve disconnection, regardless of rCBF ; therefore, there was no statistical difference in rCBF between subjects of subgroups B and G with right hemispheric

lesions. Our findings suggest that the results of the KBDT cannot be predicted with cerebral blood flow in patients with right hemispheric lesions. The reason results differ between left putamen lesions and left thalamus lesions appears to be the neural net. One side of the thalamus is connected to the contralateral cerebral cortex via the contralateral cerebellum and thalamus. A left thalamus lesion might cause hypoperfusion in the right cerebral cortex via this network.

However, when the KBDT is used to evaluate nonindependent functions, as mentioned above, which function is affected by a decrease in blood flow is unclear. For example, hypoperfusion in both frontal lobes in subjects of the low-KBDT group (group B) with a left hemispheric lesion might indicate executive dysfunction[9]. Men have been suggested to perform better than women on tasks that require rotation of spatial coordinates (such as the KBDT)[10] ; however, in this study we did not examine gender differences. Moreover, because the KBDT has not been standardized, whether the cutoff value that we established was appropriate for this purpose is unclear.

SPECT

Both CT and MRI can be used to demonstrate anatomical changes in cerebral vascular disease but cannot be used to measure or visualize blood flow. Egge et al.[11] have reported the usefulness of SPECT for predicting cognitive outcomes in subarachnoid hemorrhage, and Tamamoto et al.[12] have reported that the Barthel Index after rehabilitation correlates with rCBF before rehabilitation. These studies, including our present study, show that SPECT is useful for the clinical evaluation of stroke, although SPECT has recently been used chiefly for the rapid diagnosis or the evaluation of the progression of degenerative diseases, such as Alzheimer's disease and Parkinson's disease[13-16]. The 3DSRT version 2 is a new analytical program that uses Statistical Parametric Mapping 99 for anatomical standardization of raw images and then applies the common template to the corrected SPECT image. Therefore, this program can reduce the variability of ROIs between subjects or research studies[17].

The phenomenon in which even a small stroke within the basal ganglia produces both focal damage and a reduction in rCBF in adjacent and connected areas is known as diaschisis[18]. Diaschisis reduces cerebral blood flow via hypometabolism, may impair recovery of neural reorganization, and plays a role in poststroke neuroplasticity[19]. A PET study has shown widespread hypometabolism after subcortical infarction[20]. Therefore, evaluating cerebral blood flow after stroke is important.

This report has shown that a relationship between rCBF and cognitive function and that SPECT is useful for the evaluation of cerebral vascular disease, especially left hemispheric lesions. However, these findings shed light on only some of the factors related to the complicated subject of cognition. Whether hypoperfusion decreases cognitive function directly or whether the decrease in cognitive function secondarily causes hypoperfusion remains unclear. Now that an accurate method of examination is being established, an answer to this question may be within reach.

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