Annals of Nuclear Medicine Vol. 21, No. 1, 15–23, 2007

Decreased cerebral blood flow and prognosis of Alzheimer's disease: A multicenter HMPAO-SPECT study

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Purpose: To determine the usefulness of brain perfusion SPECT for evaluating the severity and progression of Alzheimer's disease (AD). ***Methods:*** Eighty-four AD patients were included. At entry, ^{99m}Tc-HMPAO-SPECT, the Mini Mental State Examination (MMSE), Mental Function Impairment Scale (MENFIS), and the Raven Colored Progression Matrix (RCPM) were performed for all 84 patients. During the follow-up periods, two individual MMSE evaluations in 34 patients, two MENFIS evaluations in 30 patients, and two RCPM evaluations in 20 patients were performed. Based on the regions of decreased cerebral blood flow demonstrated on 3D-SSP images of SPECT, the cases were classified as type A (no decrease), type B (decreased blood flow in the parietal or temporal lobe), type C (decreased blood flow in the frontal lobe and parietal or temporal lobe), type Pc (decreased blood flow in posterior cingulate gyrus only), and "other types". The types of decreased blood flow, scores on neuropsychological evaluations, and symptom progression were analyzed. ***Results:*** The MENFIS, MMSE, and RCPM scores were poorest in type C patients at entry. The degree of decrease of these scores during the follow-up periods was also greatest in type C. The greatest difference between patients with and without rapid progression in SPECT data of the mild AD patients (MMSE score ≥ 24) was in the frontal lobe. ***Conclusion:*** Decreased blood flow in the frontal lobe of AD patients is correlated not only with reduced cognitive function at the time of the evaluation but with rapid progression in the subsequent clinical course.

Key words: 3D-SSP, Alzheimer's disease, ^{99m}Tc-HMPAO SPECT

INTRODUCTION

Alzheimer's disease (AD) is a prevalent cause of cognitive disorder, and many researchers have reported characteristic SPECT findings of AD. While most previous studies using brain perfusion SPECT placed an emphasis on the usefulness of SPECT for early or differential diagnosis,[1,2] it is desirable for clinicians who interpret

Received March 16, 2006, revision accepted October 2, 2006.
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SPECT images of AD patients to know the relationship between SPECT findings and degree of disease severity and/or clinical prognosis. Especially, to predict clinical prognosis of AD has clinical importance, since the course of cognitive decline in AD patients is believed to be considerably variable, and rapid progression of the disease may critically lower their quality of life and may put a considerable strain on their family caregivers. We empirically know that SPECT findings are also considerably valuable among individual AD patients, while hypoperfusion is typically shown in the parietal lobes, frontal lobes, the posterior cingulate gyri. The present study using ^{99m}Tc-hexamethyl-propyleneamine oxime (HMPAO)-SPECT was conducted at 11 facilities to investigate the relationship between the decrease pattern of cerebral blood flow and the prognosis of the disease as well as disease severity.

SUBJECTS AND METHODS

Eighty-four consecutive patients (male/female = 27/57; age range 47–90 years; mean ± SD, 69 ± 8.6 years) with the diagnosis of probable AD were recruited at 11 facilities in this study. The diagnosis of probable AD was made in accordance with the stringent criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer Disease and Related Disorders Association (ADRDA). The Hachinski ischemic[3] and Manchester[4] score were determined to exclude underlying causes of dementia other than AD. Patients with a Hachinski ischemic score of 7 or above were diagnosed as having vascular-type dementia, and those with a positive Manchester score were diagnosed as having frontotemporal dementia. Both groups of patients were excluded from the study.

At entry, the Mental Function Impairment Scale (MENFIS),[5] the Mini-mental State Examination (MMSE),[6] and the Japanese version of the Raven Colored Progression Matrix (RCPM)[7] were performed in all patients to assess neuropsychological status, and ^{99m}Tc-HMPAO-SPECT was performed to evaluate cerebral blood flow in all patients. The mean scores at entry were: MENFIS, 21.2 ± 10.5; MMSE, 19.0 ± 5.8; RCPM, 22.7 ± 8.7.

Some patients underwent two individual evaluations during the follow-up study. The results for those patients were also analyzed: MMSE, 34 patients; MENFIS, 30 patients; RCPM, 20 patients. The intervals between the two evaluations were: MMSE, 609 ± 315 days; MENFIS, 611 ± 273 days; and RCPM, 496 ± 207 days. No patients had received treatment for dementia at the time of initial neuropsychological test and SPECT study. Most patients did not have treatment for dementia during the follow-up periods, whereas only 4 patients were treated with acetylcholine esterase (AChE) inhibitors.

The SPECT data of 52 healthy subjects (age; 44–78, mean age; 64.4 ± 8.9) were used as a normal database for three-dimensional stereotactic surface projections (3D-SSP) analysis. The healthy subjects had no history of neurologic or psychiatric disorders. The results of their neurologic examination and brain imaging examinations (MR imaging or CT) were normal, and their cognitive function was judged to be normal by experienced neurologists (MMSE score, 29–30).

This study protocol was approved by the ethical committee of each institution, and all patients and healthy subjects included in this study gave their informed consent.

SPECT data acquisition

A 740 MBq dose of ^{99m}Tc-HMPAO was injected intravenously, and SPECT images were acquired over a period of 15 to 30 minutes beginning 5 to 10 minutes later. The SPECT equipment and reconstruction conditions are listed in Table 1. Number of the healthy subjects/patients who underwent SPECT imaging with each equipment were: Toshiba GCA 9300, 20/35; Picker Prism 3000, 13/15; Hitachi 2000H, 17/24; Shimadzu SET 080, 1/7; Siemens Multi SPECT, 1/3. The frequency of the preprocessing filters that achieved a standard spatial resolution in reconstructed images was determined for the Toshiba 9300, Picker PRISM3000, and Hitachi 2000H models in a

Table 1 SPECT equipment and reconstruction conditions

Camera type	Pre filter	Attenuation correction	Reconstruction filter
Toshiba GCA 9300	Butterworth 0.65 cycles/cm	Chang	Ramp
Picker Prism 3000	3D post 0.24–0.26 cycles/pixel	Chang	Ramp
Hitachi 2000H	Butterworth 0.65 cycles/cm	Chang	Ramp
Shimadzu SET 080	Butterworth 20 mm	Chang	Ramp
Siemens Multi SPECT	Hanning 0.7 cycles/cm	Chang	Shepp & Logan

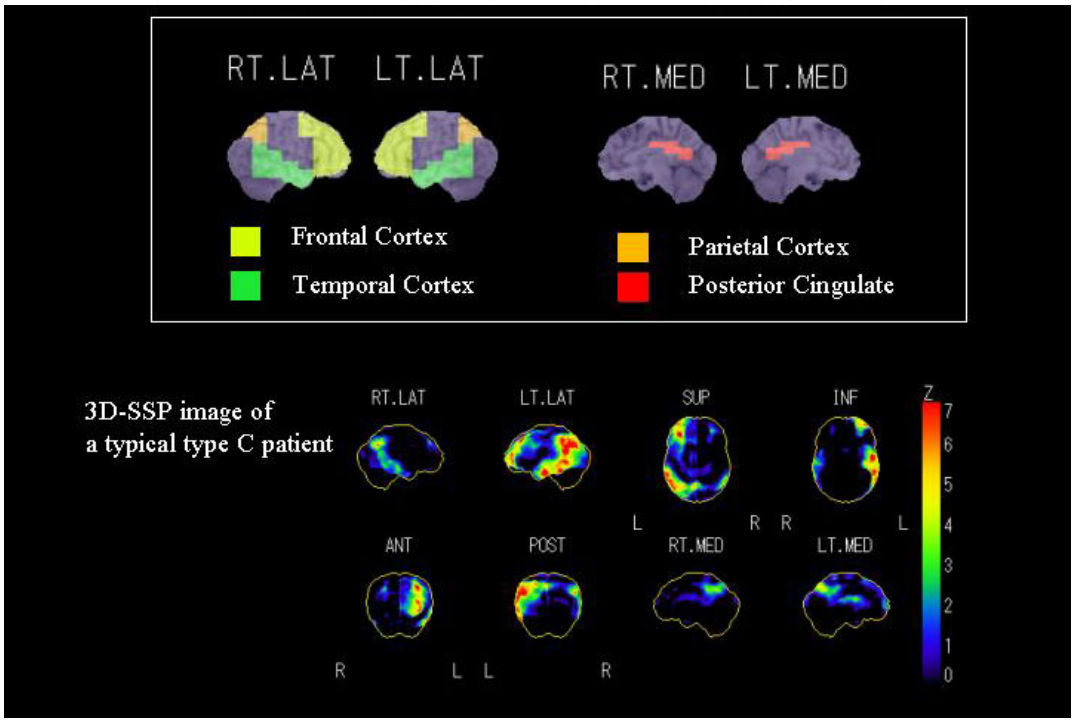

Fig. 1 Evaluated regions and typical C-type images. The regions that were included in the image interpretation. The 3D-SSP image sets of a typical type C patient.

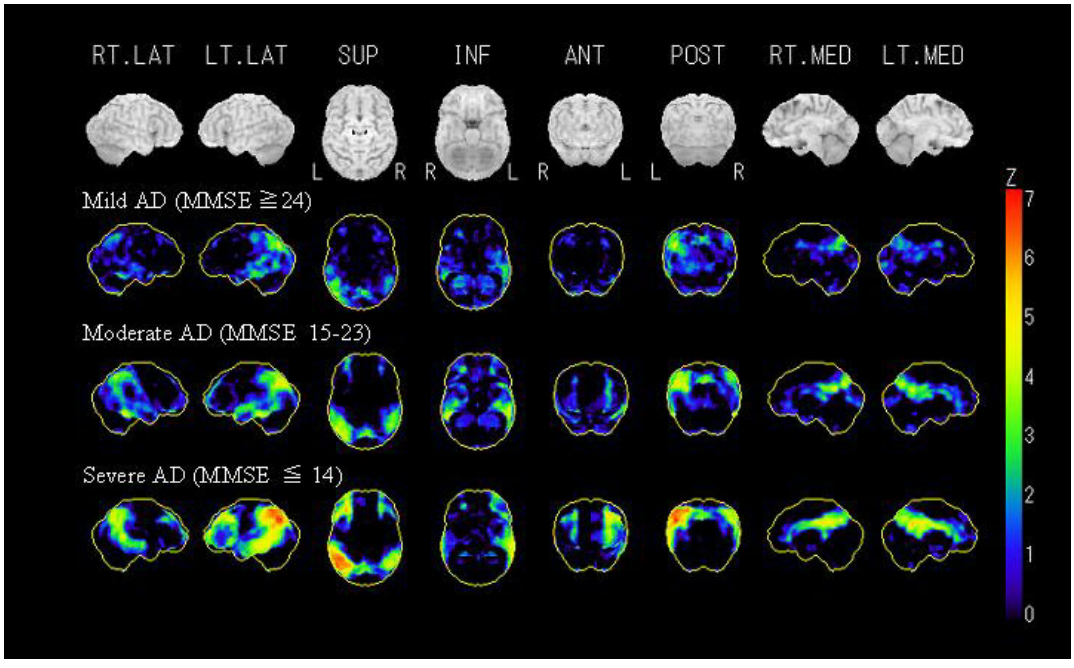

Fig. 2 Z-score images of mild, moderate, and severe AD patients. The results of two-group comparison between AD groups (mild, moderate, and severe) and the normal controls.

Table 2 Initial neuropsychological test score

type of perfusion reduction	age	MENFIS	MENFIS sub score			MMSE	RCPM
			cognitive function impairment	motivational functions impairment	emotional function impairment		
type C (n = 34)	69.7 ± 9.84	25.3 ± 10.7	16.2 ± 7.2	5.6 ± 3.1	3.2 ± 2.5	16.9 ± 6.3	18.4 ± 8.4
type B (n = 31)	69.2 ± 9.05	19.8 ± 10.3	13.2 ± 6.2	4.3 ± 3.8	1.9 ± 2.0	19.6 ± 5.3	23.5 ± 8.8
type Pc (n = 5)	71.8 ± 5.06	18.2 ± 10.9	11.4 ± 8.0	5.2 ± 2.1	1.6 ± 1.6	21.4 ± 4.2	24.8 ± 5.0
type A (n = 11)	69.0 ± 7.77	16.2 ± 6.5	9.2 ± 4.9	4.6 ± 1.8	2.3 ± 1.8	21.4 ± 4.3	27.4 ± 6.2
other type (n = 3)	72.7 ± 1.15	14.3 ± 2.1	10.0 ± 1.4	3.3 ± 0.5	1.0 ± 0.8	23.0 ± 1.6	30.7 ± 2.5

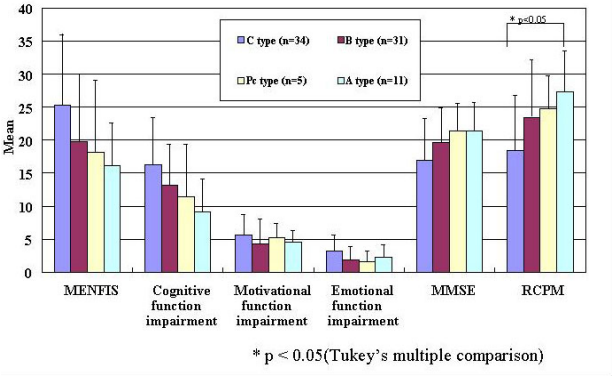

Fig. 3 Initial neuropsychological test scores in each perfusion reduction type. The results of MENFIS (total score and subscales), MMSE and RCPM scores of type A, B, C, Pc and other-types at initial examinations.

Table 3 Change in neuropsychological test scores

	type of perfusion reduction	Initial exam	1 year later
MENFIS	type A (n = 5)	17.8 ± 5.7	19.4 ± 5.5
	type B (n = 13)	18.7 ± 10.1	23.5 ± 15.4*
	type C (n = 9)	18.1 ± 7.1	31.8 ± 15.5**
MMSE	type A (n = 5)	20.2 ± 2.6	21.1 ± 2.0
	type B (n = 16)	18.5 ± 5.8	17.4 ± 5.6
	type C (n = 10)	20.4 ± 3.9	17.1 ± 4.5*
RCPM	type A (n = 3)	27.7 ± 1.2	27.4 ± 3.7
	type B (n = 11)	24.8 ± 5.6	21.7 ± 7.95
	type C (n = 4)	22.3 ± 10.0	17.6 ± 9.1

There are significant differences between scores in initial exam and those in follow-up exam
*: $p < 0.05$, **: $p < 0.01$

preliminary study and used for reconstruction of the images of the subjects studied. A Shimadzu SET080 machine and a Siemens Multi SPECT3 machine were used in one facility each, and the reconstruction conditions used during routine medical care in all facilities were applied to the subjects.

SPECT data analysis

Regions of decreased cerebral blood flow in each patient were evaluated by using 3D-SSP program developed by Minoshima et al.,[1,8–10] and the details of the 3D-SSP program are described below.

Briefly, 3D-SSP program involves three major steps. The first step consists of rotational correction and centering of the dataset in three dimensions, resulting in a realignment of the AC-PC line, and linear scaling and nonlinear warping of the data is performed to adjust the subject's brain to the proportional grid system proposed by Talairach and Tournoux,[11] resulting in a standardized image set with a uniform voxel size of 2.25 mm. Second, data extraction is performed by a method in which the cortical activity is projected onto the brain surface, and surface-projected perfusion images are obtained. In this step, the maximum pixel values on predefined vectors perpendicular to the surface and covering the entire standardized outer brain contour are determined with a search depth of 6 pixels (13.5 mm), and the maximum pixel values detected are assigned to the corresponding pixel of the standardized surface. Finally, the projected surface values obtained are compared with the normal database on a pixel-by-pixel basis, and Z-score images are obtained. A Z-score is calculated for each surface pixel: Z-score = {(normal mean) − (individual value)/(normal standard deviation)}, and regions of hypoperfusion are demonstrated as high Z-score areas on Z-score images. 3D-SSP program also allows two-group comparisons between a patient group and a normal control group, or between two patient groups.

Classification of the AD patients into groups with mild, moderate, and severe dementia

We classified the patients according to the initial MMSE score (at entry) into a group with scores of 24 or more, a group with scores of 23–15, and a group with scores of 14 or below, and performed two-group comparisons between each AD group and the healthy control group by means of the 3D-SSP program to investigate blood flow changes occurring with disease progression.

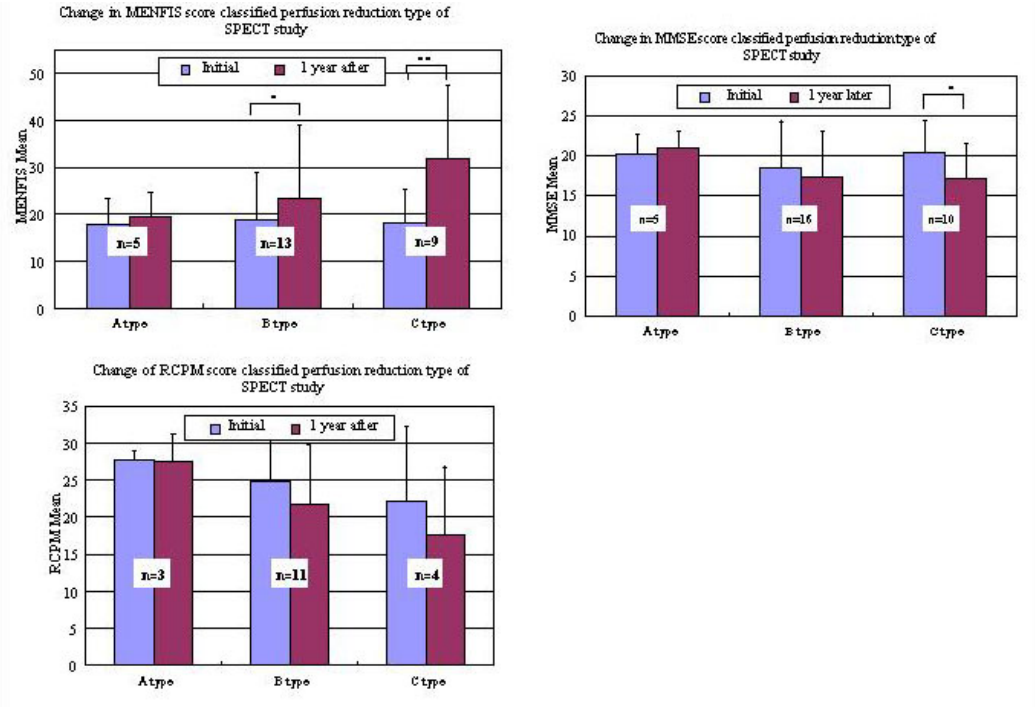

Fig. 4 Change of neuropsychological test scores in each perfusion reduction type. The changes in MENFIS, MMSE and RCPM scores in type A, B, C.

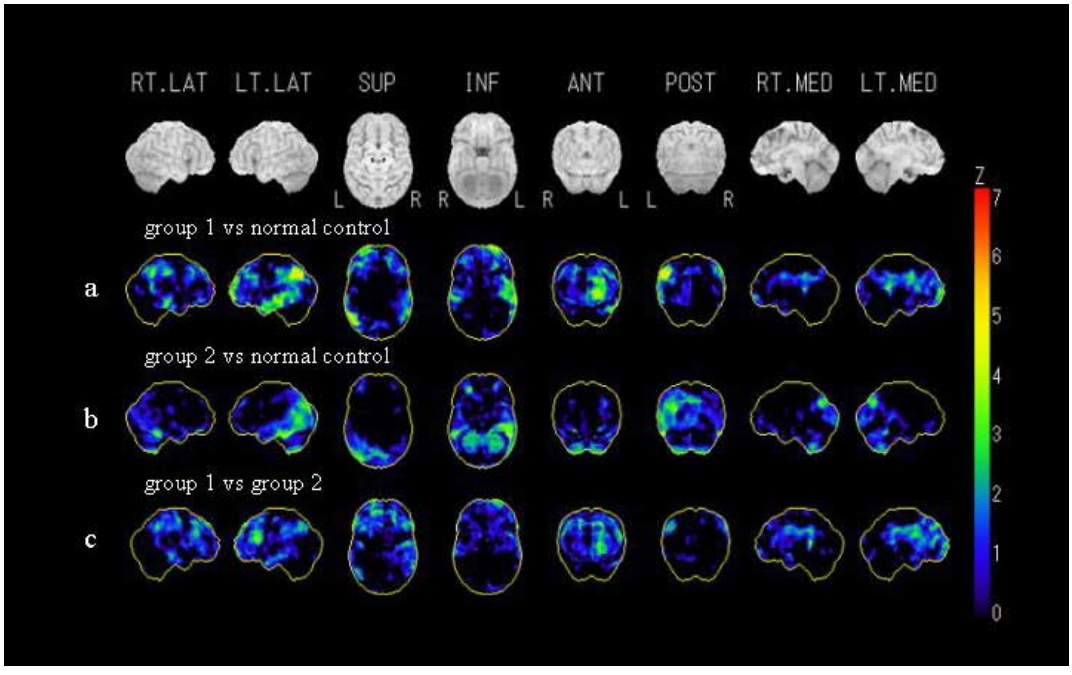

Fig. 5 Perfusion reduction in patients with mild Alzheimer's disease (initial MMSE ≥ 24). Regions of decreased cerebral blood flow on the SPECT in patients with mild disease (MMSE scores of ≥ 24). a : The results of two-group comparison between group 1 (a group with decreases in MMSE score > 3 points/year) and the normal controls. b: The results of two-group comparison between group 2 (a group with decreases in MMSE score ≤ 3 points/year) and the normal controls. c: The results of two-group comparison between group 1 and group 2, and the regions are demonstrated in which the decrease of blood flow was greater in group 1 than in group 2.

Classification of regions of decreased cerebral blood flow detected by SPECT

Cases were classified on the bases of the Z-score images as "type A", when no decrease in blood flow was observed, "type B", when blood flow in the parietal or temporal lobe was decreased; "type C", when blood flow in the frontal and parietal or temporal lobes was decreased; "type Pc", when blood flow in the posterior cingulate gyrus alone was decreased; and "other types", when not classifiable into any of the above types. The cases with hypoperfusion of the posterior cingulated gyri often have some degree of hypoperfusion of the precuneus in early AD patients. Thus, cases with hypoperfusion of the posterior cingulated gyri and precuneus and without any other hypoperfusion area were classified as Type Pc. The areas with Z-scores > 2 were evaluated as having decreased blood flow. Figure 1 shows the regions that were included in the image interpretation. We investigated the correlation between types of blood flow decrease and scores on the neuropsychological tests (initial and follow-up examinations). Since the length of the follow-up period varied among patients, in the analysis of the relationship between the SPECT findings and changes on neuropsychological scores during the follow-up period we postulated that the changes in scores were linear and converted them to changes in score per year.

Relationship between disease progression in mild AD patients and regions of decreased cerebral blood flow detected by SPECT

Sixteen patients with mild disease (MMSE score ≥ 24) were separated into the two groups according to the degree of decrease of their MMSE score: a group with decrease of the MMSE score by >3 points/year (group 1), and a group with decrease of the MMSE score by ≤3 points/year (group 2). Comparisons between the 2 groups were made by means of the 3D-SSP program.

RESULTS

Classification of the AD patients into groups with mild, moderate, and severe dementia

Based on the MMSE scores, the patients were classified as having mild, moderate, and severe AD. The 3D-SSP displays in Figure 2 show the results of two-group comparisons between the mild, moderate, and severe AD groups and the normal controls. In the mild AD group, with MMSE scores of 24 or more (n = 16), a decrease in cerebral blood flow in the parieto-temporal lobe and posterior cingulate gyrus was demonstrated. In the moderate AD group, with MMSE scores of 23–15 (n = 51), the decreases in the above regions were accentuated, and cerebral blood flow also decreased in part of the frontal lobe. In the severe AD group, with MMSE scores of 14 or below (n = 17), the decreases were further accentuated and extended to the entire frontal lobe, except the sensorimotor area.

Classification of the regions of decreased cerebral blood flow detected by SPECT

Classification into types of decreased cerebral blood flow region by 3D-SSP analysis identified 34 patients with type C, 31 with type B, 5 with type Pc, 11 with type A, and 3 with other types.

The results of MENFIS (total score and subscales), MMSE, and RCPM scores of type A, B, C, Pc, and other types at the time of the initial examinations are shown in Table 2 and Figure 3. Type C had the worst scores on all of the scales. A 4-group comparison among types C, B, Pc, and A revealed a difference in RCPM scores between type C and type A ($p < 0.05$, Tukey's multiple comparison).

Table 3 and Figure 4 show the changes in MENFIS, MMSE, and RCPM scores in type A, B, and C during the follow-up periods. The MENFIS score increased significantly in types B and C ($p < 0.05$ and $p < 0.01$, respectively) during the follow-up periods, reflecting the progression of the disease. The MMSE scores decreased significantly in type C ($p < 0.01$). Although the changes of RCPM did not reach significance in any of the types, a certain degree of decrease in RCPM score was also observed in type B and C. Only 2 patients with type Pc could be followed up. MMSE alone was performed in 1 of them (MMSE score on the initial examination; 13, 1 year later; 13) and MENFIS alone in the other (MENFIS score on the initial examination; 17, 1 year later; 18). The MMSE, MENFIS and RCPM scores of the 2 patients with other types 24.0 ± 1.0/21.3 ± 0.1, from 13.0 ± 1.0/17.2 ± 0.6, and 32.0 ± 2.0/27.5 ± 0.4 (initial examination/1 year later), respectively.

Relationship between disease progression in mild AD patients and regions of decreased cerebral blood flow detected by SPECT

Figure 5 shows the regions of decreased cerebral blood flow in the SPECT study in the patients with mild disease (MMSE scores of ≥24). They were separated into 2 groups based on the reduction in their MMSE scores: a group with decreases in MMSE score > 3 points/year (group 1; n = 6), and a group with decreases in MMSE score ≤ 3 points/year (group 2; n = 10). Figure 5a and 5b show that blood flow in the parietal lobe, and posterior cingulate gyrus decreased to a greater extent in group 1 than in group 2, and blood flow in the frontal lobe was shown only in group 1. Figure 5c shows that the greatest difference in cerebral blood flow between the two groups was in the frontal lobe, suggesting that hypoperfusion of the frontal lobe may be most strongly correlated with early progression of AD.

DISCUSSION

This multicenter study evaluated patients in various stages of AD based on neuropsychological tests, profiles of decreased cerebral blood flow on SPECT images, and disease progression based on 3D-SSP analysis. The MENFIS, MMSE, and RCPM scores at entry were poorest in the type C patients, followed in descending order by the type B, type Pc, and type A patients. The follow-up study showed that the degree of reduction of neuropsychological test scores tended to be faster in type C, type B, and type A, in descending order. Among patients with relatively mild disease, those with MMSE score reduction of >3 points/year had a greater decrease in blood flow in the frontal lobe than those with MMSE score reduction of ≤3 points/year. These findings suggest that decreased blood flow in the frontal lobe of AD patients may be correlated not only with reduced cognitive function at the time of the SPECT examination, but also with early progression in the subsequent clinical course.

In the present study, disease progression of AD was assessed by means of MENFIS, MMSE, and RCPM test scores, while only a single test was used for assessing neuropsychological status in many previous studies. MMSE has been frequently used for assessing disease severity of AD in many studies. MMSE scores, however, can reflect only a part of the neuropsychological status of an individual patient. MENFIS can evaluate not only cognitive function, but also motivational functions and emotional functions. RCPM has played an important role as an instrument to assess non-verbal intelligence and especially logical reasoning. Using several neuropsychological tests, we tried to properly assess the severity of the disease in this study, and found that type C patients had the worst score of motivational functions and emotional functions in MENFIS test, and the changes of MENFIS scores during the follow-up periods reached statistical significance in types B and C, while those of MMSE scores also reached statistical significance in type C ($p < 0.01$). This fact suggests that hypoperfusion in the frontal lobe may have some effect on motivational functions and emotional functions as well as cognitive functions of AD patients.

At the initial examination, neuropsychological test scores on all scales were the poorest in the group with decreased blood flow in the frontal lobe on the SPECT images (type C). When classified into three grades of severity based on the MMSE scores, decreased blood flow in the patients with mild disease was shown in the parieto-temporal lobes and posterior cingulate gyrus. In the moderate AD group, the decreases in the above regions were accentuated, and cerebral blood flow also decreased in part of the frontal lobe. In the severe AD group, the decreases were further accentuated and extended to the entire frontal lobe, except the sensorimotor area. The FDG-PET study by Herholz et al.[12] found that the degree of glucose metabolism in the posterior cingulate gyrus, temporo-parietal lobe, and prefrontal association areas of AD patients correlated with disease severity. The FDG-PET study by Minoshima et al.[8] found that the decrease in glucose metabolism started in the posterior cingulate gyrus/precuneus and temporal or parietal association areas and progressed to the frontal association areas. Haxby[13] and Nebu et al.[14] found that as the disease progressed from moderate to severe, glucose metabolism in the frontal lobe decreased to the same level as in the parieto-temporal lobe. Since our results are consistent with these findings, we concluded that decreased blood flow that begins in the posterior cingulate gyrus and parieto-temporal association areas and subsequently involves the frontal lobe is the cerebral blood flow profile that indicates the severity of AD.

The results of the present study suggested that the frontal lobe hypoperfusion might be correlated with early progression in the subsequent clinical course. In the present study, patients were classified according to regions of decreased cerebral blood flow, and we found that neuropsychological test scores decreased the most in type C patients in the follow-up period (Fig. 4). Brown et al.[16] reported that decreased blood flow in the frontal lobe had the greatest effect on cognitive function in AD patients. Nagahama et al.[17] classified patients with probable AD according to the degree of reduction of cognitive function (MMSE scores) into groups with slowly or rapidly progressive AD and compared their blood flow profiles. They found that rapidly progressive disease was associated with significantly decreased cerebral blood flow in the frontal lobe. Our findings did not contradict these results. There are two possible explanations for why the frontal lobe hypoperfusion correlated with the rapid progression of AD. One possibility is that patients with the frontal lobe hypoperfusion (type C patients) fundamentally had a more rapidly progressive type of AD than the other types, and in such patients the frontal lobe hypoperfusion tends to occur in the very early stage of AD. The other explanation is that the type C patients included many patients whose disease had already progressed pathologically, and the pathological progression was accompanied by a rapid decrease in the MMSE and other psychological test scores. It is difficult to clearly determine which explanation is correct. However, while Nagahama et al.[17] did not classify their subjects according to the degree of their cognitive decline, we classified the subjects into three grades of severity based on the MMSE scores and confirmed that the frontal lobe hypoperfusion correlated with the rapid disease progression even in patients with mild AD (MMSE scores of ≥24). Based on this result, we suspect that the type C patients in our study may have included many patients with the rapidly progressive type of AD.

There is limited clinical significance of the findings of the present study. Though some of the subjects underwent two individual evaluations during the follow-up study

(MMSE, 34 patients; MENFIS, 30 patients; RCPM, 20 patients), this study had a relatively small sample size for assessing the relationship between disease progression and decreased cerebral blood flow, and this may be the reason why the changes of RCPM scores did not reach statistical significance in any of the types, while the changes of MENFIS scores reached statistical significance in types B and C and those of MMSE scores reached statistical significance in type C ($p < 0.01$). This study suggests that hypoperfusion in the frontal lobe is correlated with rapid decreases in the MENFIS and MMSE scores. Further study is, however, necessary for detailed assessment of the relationship between cerebral blood flow and the changes of RCPM scores.

The present study has other limitations. Five different equipments were used for SPECT data acquisition of the AD patients and healthy controls. In addition, 4 patients (type A, 2; type B, 1; type Pc, 1) were treated with AChE inhibitors during follow-up periods. These facts, especially, AChE treatment in 4 patients, might have some effect on the results of the present study. However, no patients of type C were given any treatment during the follow-up period, and we think that the results of the present study well revealed the relationship between the frontal lobe hypoperfusion and rapid disease progression.

APOE ε4 is well known as a risk factor for AD. Hogh et al.[18] identified a difference in blood flow in the frontal association cortices between APOE ε4 positive and negative patients. The longitudinal study of Sakamoto et al.[19] found that decreased blood flow in the prefrontal area progressed more in AD patients with the ε4 genotype than in those without it. Others, however, have found no differences in the profiles of lowered glucose metabolism irrespective of the presence or absence of the APOE ε4 genotype.[20,21] We did not assess APOE ε4 in our study; however, the relationship between the APOE ε4 genotype and decreased blood flow in the frontal lobe as well as the progression of AD requires further study.

In summary, the results of this multicenter study suggest that decreased blood flow in the frontal lobe of AD patients may be correlated not only with reduced cognitive function at the time of the SPECT examination, but also with early progression in the subsequent clinical course.

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