Analysis of Regional Cerebral Blood Flow Using ^{99m}Tc-HMPAO Brain SPECT in Senile Dementia of Alzheimer Type

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국문초록

알쯔하이머형의 노인성 치매에서 ^{99m}Tc-HMPAO 뇌 SPECT를 이용한 뇌혈류분포의 분석

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알쯔하이머병 환자 11명, 우울증 환자 7명 그리고 정상 대조군 12명을 대상으로 ^{99m}Tc-HMPAO 뇌 SPECT를 이용하여 국소 뇌혈류 분포를 분석하여 다음과 같은 결과를 얻었다.

1) SPECT 소견은 정상 대조군과 우울증군에서는 모두 정상이었으나 알쯔하이머병군에서는 7명은 양측 측두엽 및 두정엽에, 3명은 편측 측두엽 및 두정엽에 그리고 1명은 전두엽에 뇌혈류 감소의 소견을 보였다.

2) 대뇌반구간 혈류분포의 변화를 비교하는 지수인 Cerebral asymmetry index는 정상 대조군에서 0.08±0.03, 알쯔하이머병군에서는 0.11±0.04 그리고 우울증군에서는 0.09±0.03으로서 세 군 간에 유의한 차이가 없었다.

3) 소뇌반구간 혈류분포의 변화를 비교하는 지수인 Percent index of cerebellar asymmetry는 정상 대조군에서 0.4±0.7%, 알쯔하이머병군에서 −0.7±0.08% 그리고 우울증군에서 −0.7±0.7%로서 세군 간에 유의한 차이는 없었다.

4) 소뇌 계수치를 대조값으로 각 영역별 혈류분포의 변화정도를 비교하는 지수인 Region to cerebellum ratio는 우울증군에서는 정상 대조군과 유의한 차이를 보이지 않았으나 알쯔하이머병군에서는 양측 두정엽과 측두엽에서 유의한 감소를 보였다($p<0.05$).

이상의 결과로 ^{99m}Tc-HMPAO 뇌 SPECT는 알쯔하이머병의 진단에 있어서 유용한 방법임을 알 수 있었다.

INTRODUCTION

Dementia is the commenst cause of disability in the older population[1]. As average age of the population shifts upward, approximately 10% of people over the age of 60 suffer from dementia and at any one time half of those are severely demented[2].

Alzheimer's disease is the most common cause of dementia. But great uncertainties remain concerning the etiology, pathology, differential diagnosis and treatment of Alzheimer's disease. So early and accurate diagnosis of Alzheimer's disease has a major impact on the progress of research of dementia.

Diagnosis of Alzheimer's disease is made by exclusion and largely on clinical ground[3]. No specific laboratory determinents exist, and brain biopsy is unjustified. The main problem occurrs when laboratory tests, including brain imaging, show no abnormality.

Psychologic depression is a common response to physical and emotional deprivation of elderly life[3,23] and is usually reversible with appropriate medical management. Frequently depression masquarades as dementia and sometimes accompanies dementia, especially associated with multiple stroke, head trauma and Huntington's chorea[3].

In patients with severe and advanced Alzhemer's disease, significant cortical atrophy and changes in ventricular size have been demonstrated by X-ray CT but efforts to use atrophy indices to differentiate patient from elderly control have yielded inconsistent result[4,5].

Measurements of local cerebral glucose metabolism by positron emission tomography (PET) have shown bilateral temporoparietal metabolic change in Alzheimer's disease[6,7,8].

Single photon emission computed tomography (SPECT) studies using ^{133}Xe inhalation method or ^{123}I-iodoamphetamine (IMP) intravenous injection method have also shown bilateral cerebral blood flow reduction in temporoparietal areas[9,10,11].

Since PFT is a specialized and expensive technique available in only a few centers, and mainly for research, it is unlikely to become widely applied to clinical diagnosis.

^{123}I-labeled amphetamine have chemical, physical and practical drawbacks for SPECT imaging such as cost and limited availability.

A new radiopharmaceutical ^{99m}Tc-HMPAO has been showen to give images of cerebral perfusion comparable to those obtained with ^{123}I-IMP[12,13] and tomographic brain images indicated that the distribution of the compound is related to regional cerebral blood flow.

The purpose of present study is to evaluate the usefulness of ^{99m}Tc-HMPAO brain SPECT for the clinical assessment and management of Alzheimer's disease.

PATIENTS AND METHOD

1. Patients

Eleven patients with Alzheimer's disease (6 men and 2 women, mean age 54yr) and 12 normal controls (8 men and 4 women, mean age 53yr) were studied (Table 1).

All normal controls were free from known cerebrovascular disease. All patients had EEG's, X-ray CT scan and appropriate laboratory evaluation to rule out other causes of dementia. The clinical diagnosis was made after neurologic and

Table 1. Distribution of Patients

Group	No. of patient	Age	
	Total (M/F)	Mean	Range
Normal control	12(8/4)	53	(49–76)
Alzheimer's disease	11 (6/5)	58	(48–75)
Depression	7 (5/2)	54	(43–65)
Total	30 (19/11)		

psychiatric evaluation[14].

2. Method

Nonradioactive freeze—dried HMPAO kit (Ceretec*) was labeled with ^{99m}Tc-HMPAO less than 30 minutes prior to injection. Ten to sixty minutes after intravenous injection of 20 to 25 mCi of ^{99m}Tc-HMPAO, SPECT data was collected with patient positioned supine and head supported so as that orbitomeatal line be vertical. Imaging was carried out with a rotating gamma camera (Rota camera system, Siemens) and dedicated computer (CDA microDELTA computer, Siemens). SPECT data acquisition required 120 projections 3° apart into 64×64 word mode matrix. Total acquisition time was 60 minutes.

The raw data were reconstructed by filtered backprojection. Reconstructed tomographic images were subjected to a nine—point smoothing and were qualitatively interpreted.

For quantitative analysis, consecutive two transverse slices of reconstructed images were added and 3 slices were selected. Each of the 3 slices was smoothed once. Among 3 slices, the lowest slice contained information from cerebellar hemispheres, the second slice contained information from the base of the cerebral hemispheres and the highest slice contained information from the rest of cerebral hemispheres.

Six pairs of symmetrical regions of interest, matching the perfusion territories of the large cerebral arteries and cerebellar hemisphere were decided. The respective slices with their corresponding regions of interest are shown on Fig 1.

From the count values of regions of cerebral hemisphere, an index which shows perfusion difference between right and left cerebral hemisphere, an index which shows perfusion difference

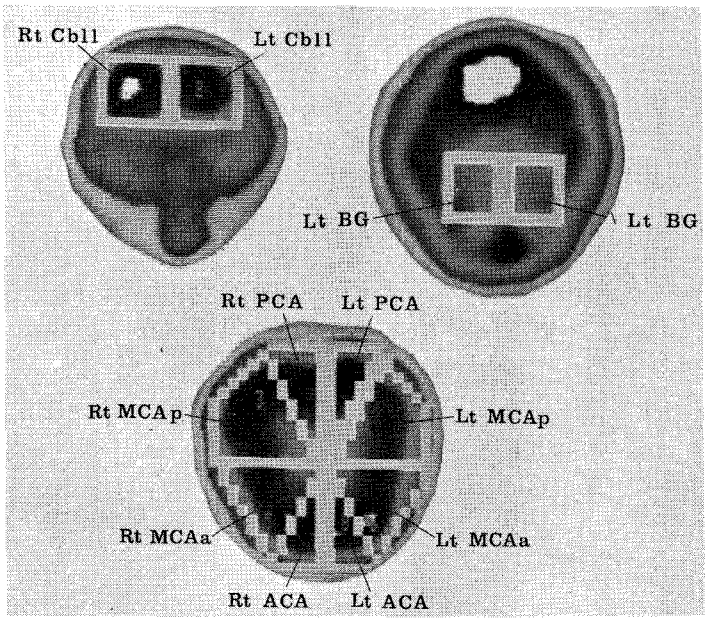

Fig. 1. Region of interest as used for quantitative analysis of SPECT images. Rt; right, Lt ; reft, Cbll ; cerebellar hemisphere, BG ; area of basal ganglia, PCA; posterior cerebral artery, MCAa ; middle cerebral artery (anterior), MCAp ; middle cerebral artery (posterior). ACA ; anterior cerebral artery.

between right and left cerebral hemisphere, cerebral asymmetry index (ASI), was calculated using following equation :

$$ASI = \sum_{i=1}^{5} [(Ri - Rio)^2]^{\frac{1}{2}}$$

where Rio is the mean normal value for the right to left ratio and Ri is right to left ratio of each patient.

From the count values in cerebellar hemispheres, an index which shows asymmetry of cerebellar uptake, percent index of cerebellar asymmetry (PIA), was calculated using following equation :

$$PIA = \frac{Cbll\ (c) - Cbll\ (i)}{Cbll\ (c)} \times 100\ (\%)$$

where Cbll (c) is count of cerebellar hemisphere contralateral to the diseased cerebral hemisphere and Cbll (i) is count of cerebellar hemisphere ipsilateral to the diseased cerebral hemisphere.

Finally region to cerebellum ratio (RCR), a ratio of the count of each cerebral region to the mean count of both cerebellar hemispheres, was calculated. Thus 5 RCR's for each cerebral hemisphere were obtained.

Table 2. Clinical Characterization of 11 Patients with Alzholmor's Disease

No.	Age	Sex	XCT	SPECT
1	49	M	Normal	Both TP
2	48	M	Normal	Both P
3	63	M	Normal	Lt FP
4	62	F	Normal	Both TP
5	60	F	Mild DA	Lt T
6	50	F	Normal	Both TP
7	53	M	Mild DA	Both T
8	75	F	Mild DA	Both P
9	54	F	Mild DA	Lt F
10	69	M	Mild DA	Lt TP
11	56	M	Mild DA	Both P

DA : Diffuse cortical atrophy, T ; Temporal lobe, P : Parietal lobe, F : Frontal lobe

RESULTS

X-ray CT findings were normal in all normal controls. Among 11 patients with Alzheimer's disese CT was normal in 6 and showed mild cortical atrophy in 5. Among 7 patients with depression, CT was normal in 5 and showed mild cortical atrophy in 1.

According to qualitative SPECT image interpretation, all normal controls and patients with depression showed normal findings. Among 11 patients with Alzheimer's disease, 7 showed reduced perfusion in both parietal and temporal areas, 3 in unilateral parietal and temporal areas and 1 in frontal area (Table 2, Table 3).

Ratios for symmetrical right to left regions of interest for each cerebral hemispheres (Rio val-

Table 3. Clinical Characterization of 7 Patients with Psychological Depression

No.	Age	Sex	X-ray CT	^{99m}Tc-HMPAO SPECT
1	48	F	Normal	Normal
2	61	M	Normal	Normal
3	65	M	Mild DA	Normal
4	50	M	Normal	Normal
5	51	M	Normal	Normal
6	60	F	Normal	Normal
7	43	M	Normal	Normal

DA : Diffuse cortical atrophy

Table 4. Normal Value for Region to Cerebellum Ratio

Region of interest	Right hemisphere		Left hemisphere	
	Mean	SD	Mean	SD
BG	0.90	0.06	0.90	0.06
PCA	0.86	0.06	0.85	0.07
MCAp	0.82	0.06	0.80	0.04
MCAa	0.79	0.05	0.78	0.05
ACA	0.81	0.05	0.81	0.04

ues) are given in Table 4. Ratios are given for territories of the anterior cerebral artery, anterior and posterior portion of middle cerebral artery and the posterior cerebral artery as well as the area of basal ganglia. HMPAO uptake is slightly higher for right hemisphere as reflected by the mean right to left ratios which are slightly above 1.

The mean and S.D. of ASI for each group is given in Table 5. The mean ASI of normal controls was 0.08±0.03, that of patients with Alzheimer's desease was 0.11±0.04 and that of patients with depression was 0.09±0.03. There was no statistically significant difference between normal controls and patient groups. Figure 2 illustrates individual ASI values for normal controls and each patients.

Table 5. Cerebral Asymmetry Index (ASI) of Each Group

Group	No. of patients	ASI		P value
		Mean	SD	
Normal control	12	0.08	0.03	
Alzheimer's disease	11	0.11	0.04	NS
Depression	7	0.09	0.03	NS

NS : Not significant

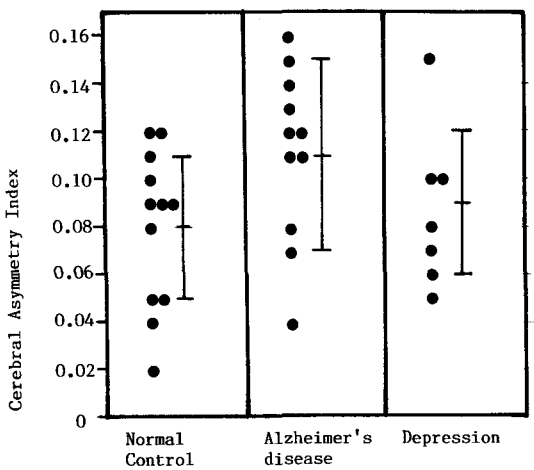

Fig. 2. Cerebral asymmetry index of each group. Dots represent individual values. Bars indicte mean ± SD.

The mean and S.D. of PIA of each group is given in Table 6. The mean PIA of normal controls was −0.4±0.7%, that of patients with Alzheimer's disease was −0.7±0.8% and that of patients with depression was −0.7±0.7%. There was no statistically significant difference between normal controls and patient groups. Figure 3 illustrates individual PIA values for normal controls and each patients.

Table 7, Table 8 and Table 9 show mean and S.D. of RCR of each region for nomal controls, patients with Alzheimer's disease and patients with depression respectively. According to 10

Table 6. Percent Index of Cerebellar Asymmetry (PIA) of Each Group

Group	No. of patients	PIA (%)		p value
		Mean	SD	
Normal control	12	−0.4	0.7	
Alzheimer's disease	11	−0.7	0.8	NS
Depression	7	−0.7	0.7	NS

NS : Not significant

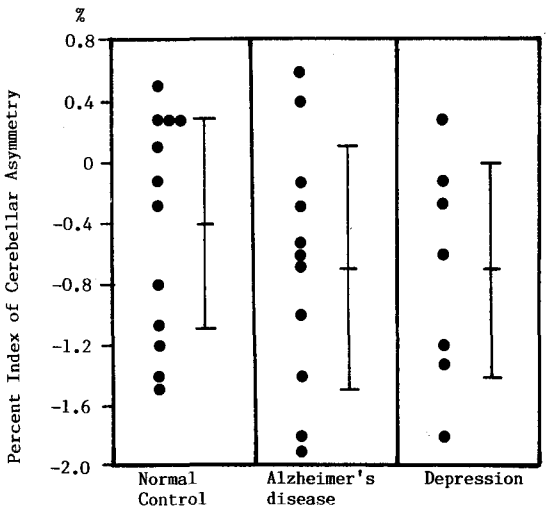

Fig. 3. Percent index of cerebellar asymmetry of each group. Dots represent individual values. Bars indicate mean ± SD.

mean RCR of patients with Alzheimer's disease, significant reduction of regional cerebral blood flow was found in the posterior portion of the middle cerebral artety territory bilaterally ($p<0.05$). The mean RCR for normal controls was 0.82 ± 0.06 for right hemisphere and 0.80 ± 0.04 for left hemisphere and that for patients with Alzheimer's disease was 0.75 ± 0.05 and 0.75 ± 0.07 respectively. All of the mean RCR's of patients with depression showed no significant difference

Table 7. Normal Value for Region to Cerebellum Ratio

Region of interest	Right hemisphere		Left hemisphere	
	Mean	SD	Mean	SD
BG	0.90	0.06	0.90	0.06
PCA	0.86	0.06	0.85	0.07
MCAp	0.82	0.06	0.80	0.04
MCAa	0.79	0.05	0.78	0.05
ACA	0.81	0.05	0.81	0.04

Table 8. Mean Region to Cerebellum Ratio of 11 Patients with Alzheimer's Disease

Region of interest	Right hemisphere		Left hemisphere	
	Mean	SD	Mean	SD
BG	0.88	0.07	0.86	0.07
PCA	0.80	0.07	0.81	0.07
MCAp	0.75*	0.05	0.75*	0.07
MCAa	0.75	0.06	0.75	0.08
ACA	0.70	0.04	0.78	0.04

* $P < 0.05$

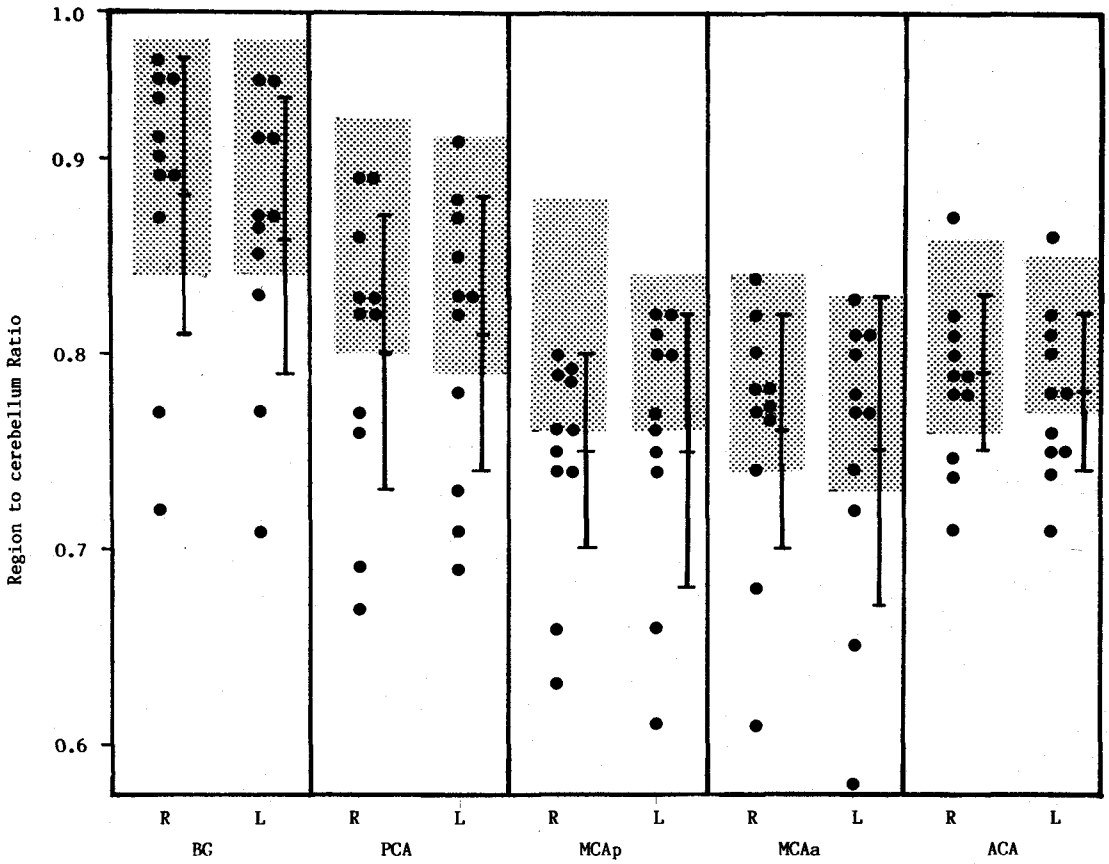

Fig. 4. Region to cerebellum ratio of 11 patients with Alzheimer's disease. Dotted areas represent normal range (mean ± SD). Bars indicate mean ± SD. of patients in each region.

from those of normal conrtrols. Figure 4 and Figure 5 illustrate individual RCR value for each patients as well as normal range.

DISCUSSION

Alzheimer's disease produces a progressive neuronal degeneration of the cerebral cortex, combiined with similar abnormalities in certain subcortical cortex. By the time of death, the temporal lobe in Alzheimer's disease is usually smaller than normal. Neuronal loss affects especially the large pyramidal cells of the hippocampus, the amygdala and the parietal and frontal association area[3]. In the early 1960s, Terry et al[15]. and Kidd[16] demonstrated that the ultrastructural changes in the brains of elderly persons with Alzheimer's disease and in those with presenile dementia were identical. Now both terms are used for the same disease irrespective of age.

Except for the signs of abnormal mental status, the physical and neurological examinations remain normal in early or intermediate state of Alzheimer's disease. Because no peripheral biochemical marker for Alzheimer's disease has been found, laboratory tests are not helpful except in a negative sense. So definite diagnosis of Alzheimer's disease can be made only if histologic confirma-

Table 9. Mean Region to Cerebellum Ratio of 7 Patients with Psychological Depression

Region of interest	Right hemisphere		Left hemisphere	
	Mean	SD	Mean	SD
BG	0.89	0.04	0.88	0.03
PCA	0.85	0.03	0.85	0.02
MCAp	0.80	0.03	0.81	0.03
MCAa	0.81	0.05	0.81	0.05
ACA	0.80	0.06	0.80	0.06

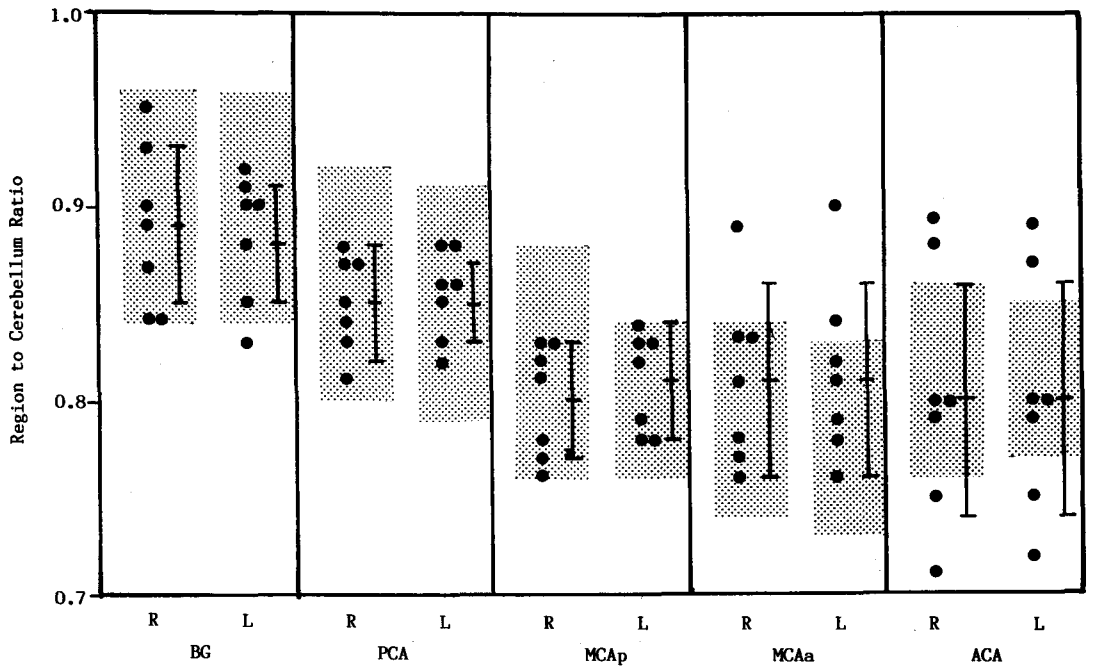

Fig. 5. Region to cerebellum ratio of 7 patients with depression. Dotted areas represents normal range (mean ± SD) Bars indicate mean ± SD. of patients in each region.

tion is obtained by performing cerebral biopsy or an autopsy[3,17]. In recent years, however, the ability to diagnose Alzheimer's disease clinically has improved greatly, from a 10 to 50% error rate[18] to at least 90% assurance of accuracy[19]. Many of the diagnostic errors recorded in earlier retrospective series were found to have resulted from the failure to recognize depression.

X-ray CT scans of brain may or may not show moderate cortical atrophy but are otherwise unremarkable[3,20]. So the diagnostic value in Alzheimer's disease of morphological changes in the brain observed by CT scan is much debated[21]. Besson et al[22]. reported that it is possible to distinguish between Alzheimer's disease, multi-infarct dementia and nondemented elderly patients by MRI studies. Undoubtedly, structural imagnig modalities such as CT and MRI are very effective for the diffrential diagnosis of dementia, establishing the presence of tumors, abscess and vascular lesions. But at this time, both CT and MRI imagings are yet regarded of limited value for the clinical assessment of Alzheimer's disease.

PET evaluations of patients with Alzheimer's disease have shown a substantial and generalized decline in oxygen in the cerebral hemisphere and in glucose utilization as the disease progresses[24,25]. There is, however, no increase in the oxygen extraction ratio, which would be expected to increase in the presence of ischemia. PET studies using ^{18}F-fluorodeoxyglucose (FDG) or ^{15}O have shown that regional cerebral metabolic rate for glucose is reduced in temporoparietal area[1].

Regional cerebral blood flow studies using ^{133}Xe[9,28], ^{123}I-IMP[2,10,11] and ^{99m}Tc-HMPAO[27,28] have also shown depressed cortical perfusion in temporoparietal area bilaterally.

Present SPECT studiy using widely available tracer ^{99m}Tc-HMPAO shows similar results with previous studies, reduced cerebral perfusion in both temporoparietal areas.

Phelps et al[34]. observed abnormalities in glucose metabolism in some patients with unipolar depression particularly in the frontal lobe of the dominant hemisphere. In most patients with depression, however, the perfusion pattern is normal in consistent with the result of present study.

Some reported that hemispheric asymmetries of cortical perfusion were found in some of patients with Alzheimer's disease[29,30,31]. Relatively better language than visuoconstructive function was associated with relatively higher left than right hemispheric regional cerbral metabolic rate for glucose. Relatively better visuoconstructive than language function was associated with relatively higher right than left hemispheric regional cerebral metabolic rate for glucose[28].

This means that the variability in the pattern of neuropsychological deficits seen in early Alzheimer's disease is due to differences between persons in the hemispheric asymmery of disease —related changes in brain physiological function. The sample of patients in present study was selected without regard to relative severity of language and visuoconstructive function. As a result, though some patients with Alzheimer's disease showed asymmetrical reduction of cerebral perfusion on SPECT images, the mean ASI resulted to be normal.

It is known that cerebellum is generally spared by major pathologic involvement in Alzheimer's disease[32,33]. Present study showed the same results that the mean PIA of patients with Alzheimer's disease was within normal range. As for that, cerebellar perfusion was chosen as a reference for cerebral perfusion change.

As is suspected, the mean RCR's of each regions for patients with depression were all normal. The mean RCR's for patients with Alzheimer's disease showed reduced regional cerebral perfusion in both temporoparietal areas in agreement with previons PET and SPECT

studies.

Some reported the presence of frontal changes in Alzheimer's disease[24,28,29,30]. Such reports, however, tend to be based on histopathological examination of end stage disease and it has been suggested that the anterior hemisphere changes observed in Alzheimer's disease may reflect a relatively late development in the course of disease. As patients in the present study cover a broad spectrum of disease severity, their demonstrations range from mild to advanced. So only 1 patient showed reduced perfusion in the frontal lobe and the mean RCR for the frontal lobe was normal.

The semiquantitative method used in the present study has been reported previously[35]. ASI is rather a compound asymmetry index and it may be somewhat more sensitive than the simple right to left ratio. The procedure of the present study, brain SPECT using ^{99m}Tc-HMPAO, is relatively unstressful and is relatively inexpensive and widely available.

As for conclusion, the brain SPECT using ^{99m}Tc-HMPAO seemed to be a valuable method for the clinical assessment and management of patients with Alzheimer's disease.

CONCLUSION

^{99m}Tc-HMPAO brain SPECT studies were performed in 11 patients with Alzheimer's disease, 7 patients with psychological depression and 12 normal controls. Changes of regional cerebral blood flow was semiquantitatively analyzed and the results were as follows.

1) In 11 patients with Alzheimer's disease, significant reduction of regional cerebral blood flow was found in both temporoparietal areas.

2) Relative perfusion between cerebral hemispheres was rather symmetrical in patient with Alzheimer's disease.

3) All patients with depression showed normal SPECT findings.

As for conclusion, ^{99m}Tc-HMPAO brain SPECT seemed to be a valuable method for clinical assessment and management of patients with Alzheimer's disease.

REFERENCES

1) NIH Conference: *Brain imaging: Aging and dementia. Ann Int Med 101:355-369, 1984*
2) Sharp P, Gemmell H, Cherryman G, et al: *Application of iodine-123-labeled isopropylamine imaging to the study of dementia. J Nucl Med 27:761-768, 1986*
3) Wyngaarden JB, Smith LH: *Textbook of medicine. 18th ed. WB Saunders, Philadelphia, 2087-2091, 1988*
4) Huges CP, Gado M: *Computed tomography and aging of the brain. Radiology 139:391-396, 1981*
5) Brinkman SD, Sarwar M, Levin HS, et al: *Quantitative indices of computed tomography in dementia and normal aging. Radilogy 138:89-92, 1981*
6) Friedland RP, Budinger TF, Ganz E, et al: *Regional cerbral metabolic alterations in dementia of Alzheimer type: Positron emission tompgraphy with [^{18}F] fluorodeoxyglucose. J Comput Assist Tomogr 7: 590-598, 1983*
7) Friedland RP, Brun A, Budinger T: *Pathological and positon emission tomographic correlations in Alzheimer's disease. Lancet 1:288, 1985*
8) Cutler NR, Haxby JV, Duara R, et al: *Brain metabolism as measured with positron emission tomography: Serial assessment in a patient with familial Alzheimer's disease. Neurology 35:1556-1561, 1985*
9) Celsis P, Agniel A, Puel M, et al: *Focal cerebral hypoperfusion and selective cognitive deficit in dementia of Alzheimer type. J Neurol Neurosurg Psychiatry 50:1602-1612, 1987*
10) Cohen MB, Graham S, Lake R, et al: *Diagnosis of Alzheimer's disease and multiple infarct dementia by tomographic imaging of iodine-123 IMP. J Nucl Med 27:769-774, 1986*
11) Lindoro J, Castro J Cruz F, et al: *Single photon emissiom tomography with ^{123}I-isopropylamphetamine in Alzheimer's disease and multi-infarct dementia. Lancet 1:1348, 1984*

12) Nowotnik DP, Canning LR, Cumming SA, et al: *Development of a ^{99m}Tc-labeled radiopharmaceutical for cerebral blood flow imaging. Nucl Med Commun 6:499-506, 1985*

13) Ell PJ, Hocknell JML, Jarritt PH, et al: *A ^{99m}Tc-labeled radiopharmaceutical for the investigation of cerebral vascular disease. Nucl Med Commun 6: 437-441, 1985*

14) McKhann G, Drachman D, Folstein M, et al: *Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology 34:939-944, 1984*

15) Terry RD, Gonatas NK, Weiss M: *Ultrastructural studies in Alzheimer's presenile dementia. Am J Pathol 44:269-297, 1964*

16) Kidd M: *Paired helical filaments in electron microscopy of Alzheimer's disease. Nature 197:192-193, 1963*

17) Katzman R: *Alzheimer's disease. N Engl J Med 314:964-973, 1986*

18) Garcia CA, Reding MJ, Blass JP: *Overdiagnosis of dementia. J Am Geriatr Soc 29:407-410, 1981*

19) Ron MA, Toone BK, Garralda ME, et al: *Diagnostic accuracy in presenile dementia. Br J Psychiatry 134: 161-168, 1979*

20) Gado M, Hughes C, Naidich T, et al: *Atrophy versus aging, abstracted. J Comput Assist Tomogr 3:563 -565 1979*

21) Naeser MA, Gebhardt C, Levine HL: *Decreased computerized tomography numbers in patients with presenile dementia. Detection in patients with otherwise normal scans. Arch Neurol 37:401-409, 1980*

22) Besson JAO, Corrigan FM, Ashcroft GW, et al: *Nuclear magnetic resonance II: Imaging in dementia. Br J Psychiatry 146:31-35, 1985*

23) Holman L: *Perfusion and receptor SPECT in the dementia. George Taplin memorial lecture. J Nucl Med 27:855-860, 1986*

24) Frackowick RSJ, Pozzilli C, Legg NJ, et al: *Regional cerebral oxygen supply and utilization in dementia: A clinical and physiological study with oxygen-15 and positron tomography. Brain 104:753 -778, 1981*

25) Foster NL, Chase TN, Mansi L, et al: *Cortical abnormalities in Alzheimer's disease. Ann Neurol 16:649-654, 1984*

26) Komatani A, Yamaguchi K, Sugai Y, et al: *Assessment of demented patients by dynamic SPECT of inhaled xenon-133, J Nucl Med 29:1621-1626, 1988*

27) Neary D, Snowden JS, Shields R, et al: *Single photon emission tomography using ^{99m}Tc-HMPAO in the investigation of dementia. J Neurol Neurosurg Psychiatry 50:1101-1109, 1987*

28) Perani D, Di Piero V, Valla G, et al: *Technetium-99 m HMPAO SPECT study of regional cerebral perfusion in early Alzheimer's disease. J Nucl Med 29: 1507-1514, 1988*

29) Foster NL, Chase TN, Fedio P, et al: *Alzheimer's disease: focal cortical changes shown by positron emission tomography. Neurology 33:961-965, 1983*

30) Duara R, Grady C, Haxby J, et al: *Positron emission tomography in Alzheimer's disease. Neurology 36: 879-887, 1986*

31) Haxby JV, Duara R, Grady CL, et al: *Relations between neuropsychological and cerebral metabolic asymetries in early Alzheimer's disease. J Cerebr Blood Flow Metab 5:193-200, 1985*

32) Brun A, Englund E: *Regional pattern of degeneration in Alzheimer's disease: Neuronal loss and histopathological grading. Histopathology 5:549-564, 1981*

33) Johnson KA, Mueller ST, Walshe TM, et al: *Cerebral perfusion imaging in Alzheimer's disease. Use of SPECT and I-123 IMP. Arch Neurol 44:165 -168, 1987*

34) Phelps ME, Mazziota JC, Baxter L, et al: *Positron emission tomography study of affective disorders-Problem and strategies. J Neurol Sci 7:331-356, 1970*

35) Lee MC, Lee MH, Koh CS, et al: *Quantitative analysis of regional cerebral blood flow using ^{99m}Tc-HMPAO SPECT in cerebrovascular disease. Kor J Nucl Med 22:15-19, 1968*