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Comparison of I-123 IMP and Tc-99m HMPAO SPECT studies with PET in dementia

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We compared I-123 IMP and 99m-Tc HMPAO SPECT studies with 0–15 H_2O and F-18 FDG PET studies, and evaluated the clinical significance of SPECT studies in dementia. Seventeen patients including 9 patients with Alzheimer's disease, 3 patients with Pick's disease and 5 patients with multi-infarct dementia were studied. IMP and HMPAO SPECT studies could not detect mildly affected areas when compared with FDG PET. However, they revealed decreased perfusion in the bilateral parietal regions in Alzheimer's disease and in the bilateral frontal regions in Pick's disease, while MRI and/or CT showed mild to moderate cerebral atrophy. IMP and HMPAO SPECT studies can be easily performed in clinical practice, and these findings were useful in the differential diagnosis of dementia. Our preliminary results suggested that SPECT studies with I-123 IMP and Tc-99m HMPAO, despite their limitations, are useful in the differential diagnosis of dementia.

Key words: Emission Computed Tomography, Dementia

INTRODUCTION

Single photon emission computed tomography (SPECT) can easily demonstrate the cerebral perfusion pattern with recently developed radiopharmaceuticals such as I-123 isopropyliodoamphetamine (IMP)[1] and Tc-99m hexamethylpropylene amine-oxime (HMPAO).[2] Until now, many studies of cerebral perfusion and metabolism in dementia have been carried out by using positron emission tomography (PET)[3–8] or SPECT.[9–16] PET is an excellent modality to study the functional changes in the brain. However, this requires an inbuilt cyclotron, auto-synthesis system and manpower. On the other hand, SPECT can be easily performed with commercially available radiopharmaceuticals. We compared IMP and HMPAO SPECT studies with PET and evaluated the clinical significance of SPECT studies in dementia.

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MATERIALS AND METHODS

Seventeen patients—9 patients with Alzheimer's disease, 3 patients with Pick's disease and 5 patients with multi-infarct dementia—were studied. These diagnoses were made clinically as well as by CT and/or MRI. Alzheimer's disease was diagnosed according to DSM-III criteria[17] for primary degenerative disorders. The diagnosis of Multi-infarct dementia (MID) was made by Hachinski's ischemic score.[18] There was no difference in age distribution in the dementia groups.

SPECT was carried out with a rotating gamma camera (Siemens LFOV-E) with a spatial resolution of 20 mm FWHM. Scans started 15 min after the administration of I-123 IMP (3–6 mCi, Nihon Mediphysics, Japan) or Tc-99m HMPAO (10–20 mCi, Amersham International plc, England). I-123 was produced by the I-127 (p, 5 n) Xe 123 reaction and contained more than 99.7% I-123. The radiochemical purity of the I-123 IMP was over 95%. Tc-99m HMPAO contained only d, l isomers and the radiochemical purity was over 94%. Tc-99m HMPAO was injected within 30 min after preparation. SPECT data were collected in 72 projections in a 64×64

matrix. Sampling time was 30 sec/projection and the total SPECT time was 36 min. SPECT images were reconstructed by filtered backprojection with a Shepp-Logan filter. Attenuation correction was done with an elliptical patient outline and attenuation factor of 0.15.

PET was performed with a HEADTOME-III (Shimadzu Corporation and Akita Noken, Japan) device with a spatial resolution of 8.2 mm FWHM. A transmission scan with a $^{68}Ge/^{68}Ga$ ring source was obtained for each patient for attenuation correction. PET data were corrected in a 128×128 matrix. Regional CBF was measured by the 0–15 steady-state method[19,20] using continuous infusion of 0–15 H_2O at a speed of 4 mCi/min through a vein in the forearm. When a steadystate was achieved on the radioactivity monitor for the head, five cross sectional planes were simultaneously scanned for 6 min at levels of 20, 35, 50, 65 and 80 mm above the orbito-meatal line. During a scan, arterial blood was drawn every 2 min. Regional CMRGlc was measured by the FDG method.[21,22] Three to 8 mCi of F-18 FDG was injected and arterial blood was drawn every 15 sec for 3 min, then every 30 sec for 6 min and at intervals of 1–10 min thereafter. The scan was started 40–60 min after the administration of the radiopharmaceutical and the data were collected for 10 min at the same levels described above for the 0–15 H_2O PET study. PET images were recostructed by fitered backprojection with a Ramachadran filter convoluted with a Butterworth filter (cutoff 8 and order 2). The interval between SPECT and PET studies was within a month for each patient. Not all SPECT and PET examinations could be performed in all patients, but IMP SPECT and FDG PET studies were performed in all patients with Alzheimer's disease.

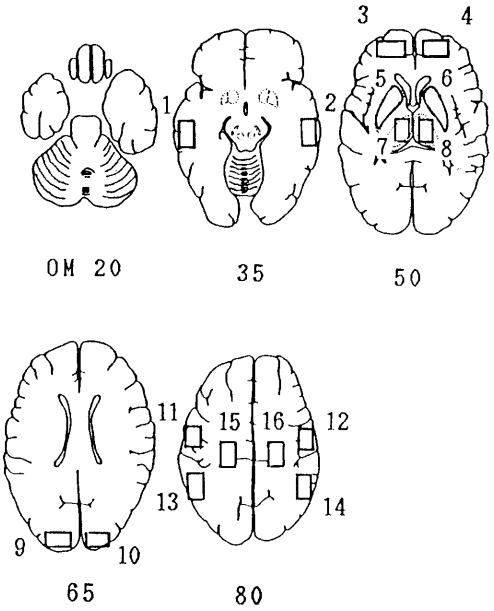
rCBF and rCMRGlc values were obtained by means of regions of interest (ROIs) of 18×14 mm or 14×14 mm in dimensions located in the frontal, temporal, occipital, parietal and primary motor (or sensory) cortices, and striatum, thalamus and sentrum semiovale on both sides (Fig. 1). The global values for the cerebral hemisphere were also obtained at the 50 mm level of the orbitomeatal line. The radioactivity/pixel in IMP and HMPAO SPECT were obtained for the same regions with ROIs in dimensions of 21×15 mm or 15×15 mm, respectively. We used the value for the primary motor area as a reference standard and compared SPECT with PET according to the count rate ratios of different regions (ROIs/primary motor cortex). The correction for cerebral atrophy was not performed.

The ratios were also obtained in normal controls in the same way as in patients with dementia and used in the evaluation of frontal, temporal and parietal abnormality. We used normal volunteers as normal controls for PET. As normal controls for SPECT, we used patients with mild neurological symptoms who were finally diagnosed by CT, MRI and PET as not having organic lesions. The ratios (mean$\pm$SD) in the frontal, temporal and parietal regions were 0.98 ± 0.07, 0.97 ± 0.04 and 1.00 ± 0.10 for IMP SPECT (n=4, mean age$\pm$S.D. was $61.8 \pm$ 12 years old), 0.95 ± 0.06, 0.97 ± 0.04 and 0.95 ± 0.03 for HMAO SPECT (n=5, 54.2 ± 14 y.o.), 1.03 ± 0.11, 1.05 ± 0.05 and 1.08 ± 0.09 for H_2O PET (n=8, 32.2 ± 6.5 y.o.), and 1.04 ± 0.07, 0.97 ± 0.05 and 1.07 ± 0.08 for FDG PET (n=5, 58 ± 5.3 y.o.), respectively. Areas with ratios below the mean-2 S.D. for normal controls were regarded as significantly abnormal.

The ratios obtained in different examinations in patients with dementia were also compared. The global values for rCBF and rCMRGlc in patients were also compared with those in controls by Student's t-test and Welch's t-test with unequal variance.

RESULTS

PET and SPECT studies show abnormalities mainly in the frontal, temporal and parietal cortices although CT and MRI showed mild to moderate cerebral atrophy in dementia. FDG PET could detect most of the lesions that can not be detected by other modalities.



1–2: Temporal 9–10: Occipital
3–4: Frontal 11–12: Primary motor
5–6: Striatum 13–14: Parietal
7–8: Thalamus 15–16: Centrum semiovale

Fig. 1 Location of regions of interest.

Table 1 Results of CT, MRI, SPECT and PET in patients with dementia

Clinical diagnosis	Age (Y)	Sex	Severity of dementia	Findings of CT or MRI	Areas of decreased CBF or CMRGlc			
					SPECT		PET	
					^{123}IMP	^{99m}Tc-HMPAO	$H_2{}^{15}O$	^{18}FDG
Alzheimer's disease	56	F	moderate	mild atrophy on CT and MRI	F,T,P (f,t,p)	—	—	F,T,P (f,t,p)
	57	F	moderate	mild atrophy on CT and MRI	T,P (t,p)	P (t,p)	P (p)	T,P (t,p)
	58	F	moderate	mild strophy on CT and MRI	P (t,p)	—	T,P (t,p)	T,P (t,p)
	55	M	moderate	mild atrophy on CT and MRI	*	P (p)	P (t)	T,P (t,p)
	58	F	moderate	mild atrophy on CT and MRI	*	—	F,T,P (t)	F,T,P (f,t,p)
	55	F	severe	moderate atrophy on CT and MRI	F,T,P (f,t,p)	*	F,T,P (f,t,p)	F,T,P (f,t,p)
	61	M	severe	mild atrophy on CT and MRI	T,P (t,p)	T,P (t,p)	—	F,T,P (f,t,p)
	64	F	severe	moderate atrophy on CT and MRI	P (p)	P (p)	T,P (f,p)	F,T,P (f,t,p)
	58	M	severe	mild atrophy on CT	P (p)	—	*	F,T,P (f,p)
Pick's disease	71	F	moderate	mild atrophy on CT and MRI	F (f)	—	F (f,t)	F,T,P (f,t,p)
	60	F	moderate	mild atrophy on CT	—	F (f)	F (f,t)	F,T (f,t)
	62	F	severe	moderate atrophy on CT	F (f)	—	—	F,T (f,t)
Multi-infarct dementia	73	F	moderate	multiple infarcts on CT and MRI	F,T (f,t)	—	F,T (f,t)	F,T (f,t)
	64	M	moderate	multiple infarcts on CT	T,P	—	P	T,P (t,p)
	57	M	severe	large infarct in lt. temporal on CT	P	—	P	—
	53	M	severe	diffuse white matter lesion on MRI	*	—	*	(p)
	75	M	severe	diffuse white matter lesion on MRI	—	P (p)	T (t)	—

F: Lt. frontal, T: Lt. temporal, P: Lt. parietal, (f): Rt. frontal, (t): Rt. temporal, (p): Rt. parietal

*: no area with significant reduction, —: not examined

Table 1 shows the results of SPECT and PET studies in each patient as well as CT and MRI findings. The abnormalities were diagnosed on the basis of the ratios (ROIs/primary motor area). However, quantitative values in PET studies were not considered in this table. The IMP SPECT study detected 27 lesions out of 54 sites observed in 9 patients with Alzheimer's disease, HMPAO SPECT 11 lesions out of 30 sites in 5 patients, H_2O PET 23 lesions out of 42 sites in 7 patients and FDG PET 47 lesions out of 54 sites in 9 patients. In Pick's disease, IMP SPECT study detected 4 lesions out of 12 sites, HMPAO SPECT 2 lesions out of 6 sites, H_2O PET 6 lesions out of 12 sites, FDG PET 14 lesions out 18 sites. In MID, the IMP SPECT study detected 7 lesions out of 24 sites observed, HMPAO SPECT 2 lesions out of 6 sites, H_2O PET 8 lesions out of 30 sites and FDG PET 9 lesions out 18 sites.

In Alzheimer's disease, decreased perfusion or metabolism in both parietal regions was detected in 7 of 9 cases by IMP SPECT, 4 out of 5 cases by HMPAO SPECT, 4 out of 6 cases by H_2O PET and all of 9 cases by FDG PET. In Pick's disease, decreased perfusion or metabolism in the bilateral frontal regions was detected in both of 2 cases by IMP SPECT, one case by HMPAO SPECT, both of 2 cases by H_2O PET and all of 3 cases by FDG PET.

Figure 2 shows the correlation between the ratios (ROI/primary motor area) for rCBF (F/Fr) and rCMRGlc (G/Gr) measured by PET in 13 patients (208 regions) with dementia. They were well-correlated ($r=0.84$). Fig. 3 shows the correlations between the ratios for the SPECT and H_2O PET studies. The count rate ratios (C/Cr) in IMP (12 patients, 192 regions) and HMPAO SPECT (6 patients, 96 regions) studies were significantly correlated with those for rCBF in the PET study. However, both SPECT studies overestimated the low count area and also underestimated the high count area compared to PET.

The count rate ratios (parietal cortex/primary motor area and frontal cortex/primary motor area) are compared with SPECT and PET in Table 2. The

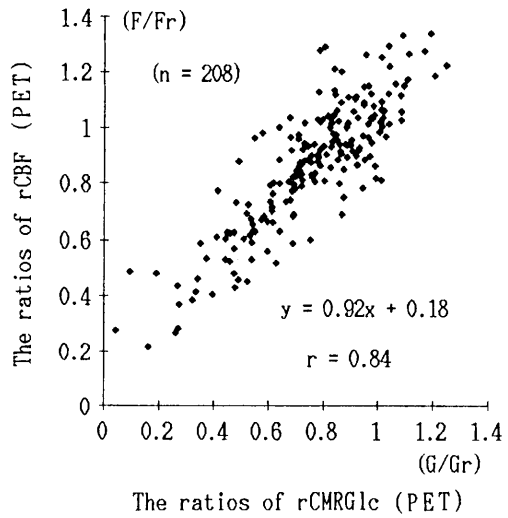


Fig. 2 Correlation of the ratios (ROI/primary motor area) in rCBF (F/Fr) and rCMRGlc (G/Gr) measured by PET in 13 patients (208 regions) with dementia. They were well correlated.

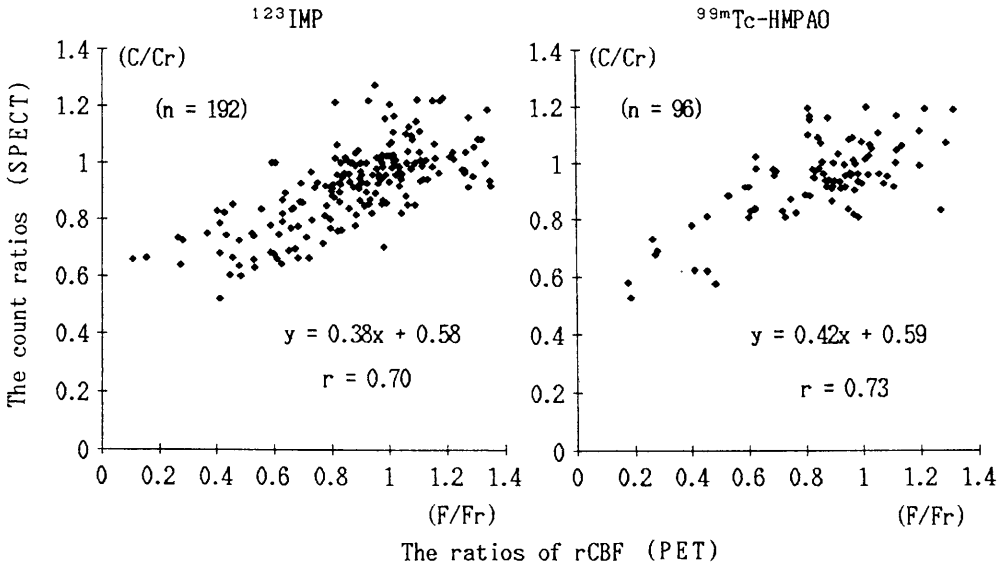


Fig. 3 Correlation of the ratios in SPECT and $H_2{}^{15}O$ PET studies in dementia. The count rate retios (C/Cr) in IMP (12 patients, 192 regions) and HMPAO SPECT (6 patients, 96 regions) studies were significantly correlated with those of rCBF (F/Fr) in the PET study.

Table 2 Comparison of ratios (parietal/primary motor area or frontal/primary motor area) in different examinations

Clinical diagnosis	The ratios (ROIs/PM)			
	SPECT		PET	
	^{123}IMP	^{99m}Tc-HMPAO	$H_2{}^{15}O$	^{18}FDG
AD (P/PM ratio)	0.75±0.10 (n=9)	0.86±0.03 (n=5)	0.69±0.11 (n=6)	0.57±0.15 (n=9)
PD (F/PM ratio)	0.74±0 (n=2)	0.81 (n=1)	0.72±0.01 (n=2)	0.59±0.03 (n=3)

(mean±SD)
AD: Alzheimer's disease, PD: Pick's disease, P: parietal cortex, F: frontal cortex, PM: primary motor area
**: $p<0.025$, ****: $p<0.005$ (Significant difference between examinations)

Table 3 Global CBF and CMRGlc values in dementia

Clinical diagnosis	Global CBF and CMRGlc values	
	CBF (ml/min/100 ml)	CMRGlc (mg/min/100 ml)
AD	(n=6) 24.7±3.9***	(n=9) 4.3±0.9***
PD	(n=2) 24.6±3.4*	(n=3) 5.0±0.8
MID	(n=5) 23.1±3.2***	(n=3) 4.1±0.3**
Controls	(n=8) 35.2±7.7	(n=4) 6.5±0.9

(mean±SD)
AD: Alzheimer's disease, PD: Pick's disease
MID: multi-infarct dementia
*: $P<0.05$, **: $P<0.025$, ***: $P<0.01$ (Significant reduction compared with controls)

parietal/primary motor area ratio showed higher contrast in the FDG PET study. The ratio in the IMP SPECT study was similar to that in the H_2O PET study. The HMPAO SPECT study showed lesser contrast.

Table 3 shows global values for CBF and CMRGlc in patients with dementia and in controls. CBF and CMRGlc in dementia were significantly decreased when compared with those in controls.

The FDG PET, IMP SPECT and HMPAO SPECT images of a 61-year-old male with Alzheimer's disease are shown in Fig. 4. Regional CMRGlc and cerebral perfusion are decreased in the fronto-temporo-parietal regions. The cerebellum, striatum, primary visual and motor cortices are relatively spared. The HMPAO SPECT images show lower contrast than the IMP SPECT.

Figure 5 shows the FDG PET, H_2O PET and HMPAO SPECT images of a 60-year-old female with Pick's disease. Regional CMRGlc and cerebral perfusion are decreased mainly in the medial aspect of the frontal region on both sides.

DISCUSSION

SPECT is easy to use in routine clinical practice, however, it is still inferior to PET in spatial resolution and quantification. To evaluate the clinical significance of SPECT studies, we compared SPECT with PET by a semiquantitative method which took into account the count rate ratios for different regions (ROIs/primary motor cortex). As shown in Fig. 2 and 3, the ratios (ROI/primary motor area) for rCBF were well-correlated with those for rCMRGlc, and the ratios in IMP and HMPAO SPECT studies were also significantly correlated with those for rCBF in the PET study. We can therefore obtain information on cerebral metabolism in dementia by IMP and HMPAO as well as information on cerebral circulation, although there are some limitations.

In the present study, we used the primary motor area as a reference standard, although the previous investigators used the cerebellum as a reference.[13,15] This is because the primary motor area is usually spared in primary degenerative dementia in contrast to the parietal cortex,[5] where rCBF and rCMRGlc decrease severely, and both areas can be observed in a single slice.

Among 4 kinds of studies, FDG PET showed the highest degree of detection of abnormal regions, and IMP and HMPAO SPECT studies could not detect mildly affected areas efficiently (e.g., the frontal regions in Alzheimer's disease). As shown in Table 2, FDG PET showed pronounced variation in the parietal/primary motor cortex ratio and this may be a reason for higher detectability as well as higher

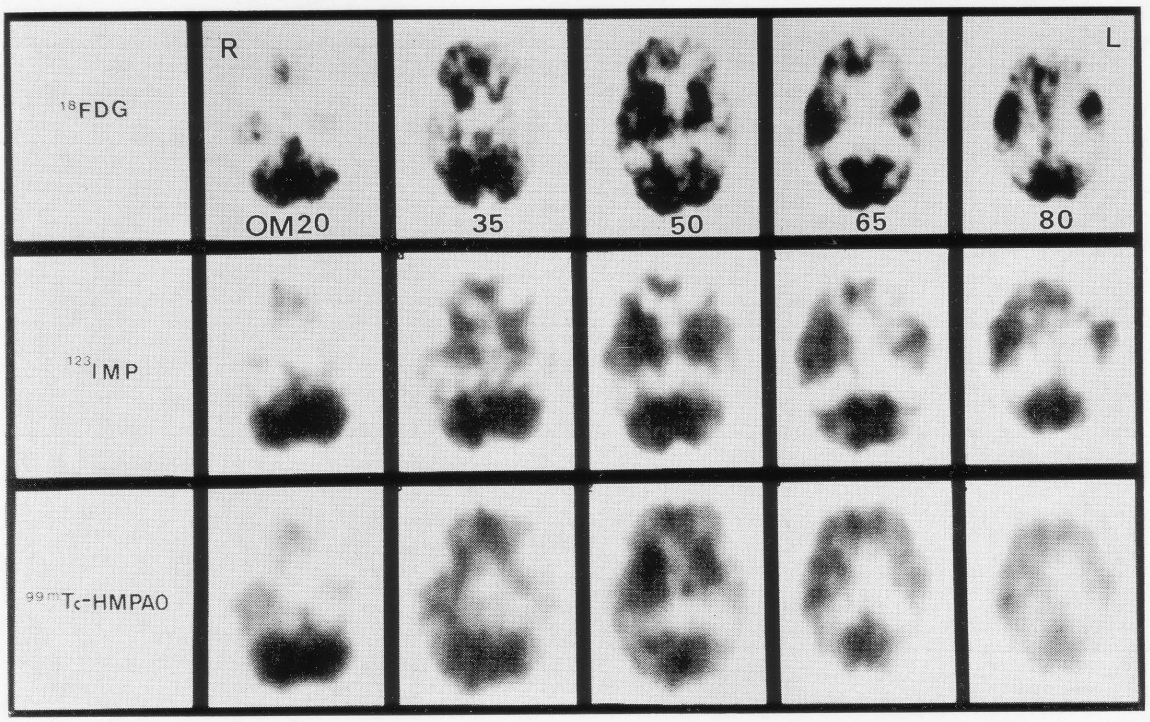


Fig. 4 (Alzheimer's disease, 61-year-old male) (F-18 FDG PET, I-123 IMP SPECT and Tc-99m HMPAO SPECT images show decreased CMRGlc and perfusion in the fronto-temporo-parietal regions on both sides. The cerebellum, striatum, primary visual and motor cortices are relatively spared. HMPAO SPECT images show less contrast than I-123 IMP SPECT.

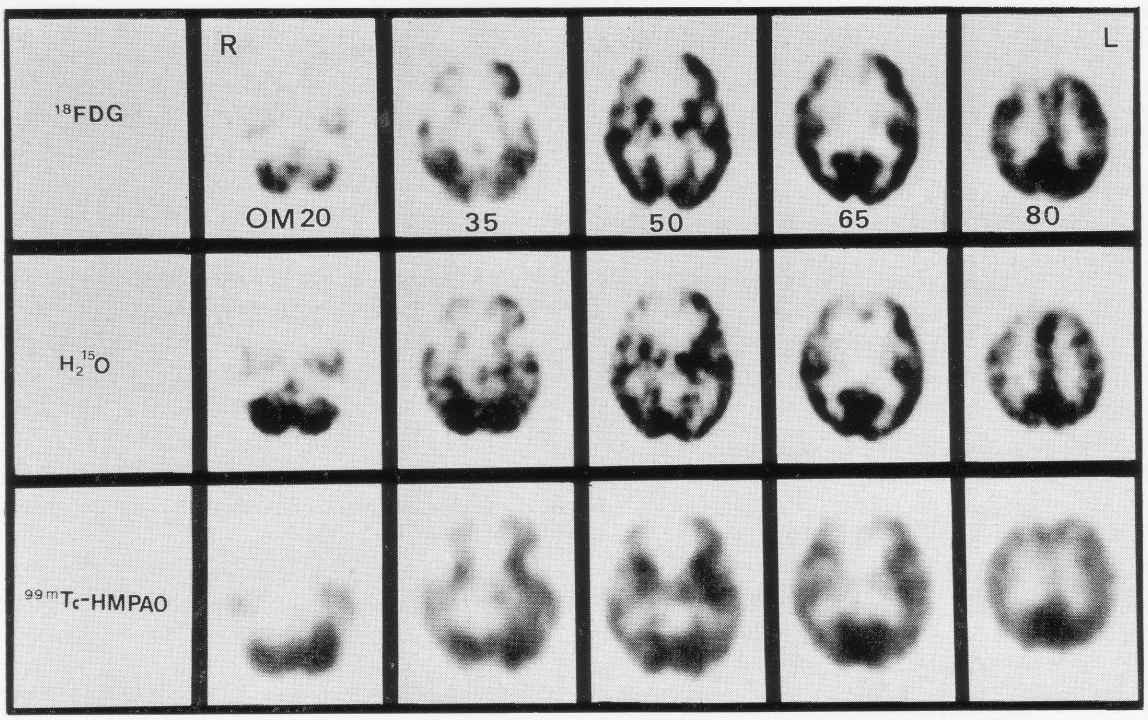


Fig. 5 (Pick's disease, 60-year-old female) F-18 FDG PET, 0–15 H_2O and Tc-99m HMPAO SPECT images show decreased CMRGlc and perfusion in the frontal region on both sides.

resolution of the PET device. H_2O PET was slightly inferior to FDG PET. The difference in detection in FDG and H_2O PET studies may be due to the lower contrast of the rCBF values calculated by the 0–15 steady-state method. HMPAO SPECT had the least variation in the ratio. According to a previous report,[14] HMPAO SPECT was inferior to IMP SPECT in the detection of abnormal regions in dementia. Our results are consistent with these reports, and one must be careful in the interpretation of HMPAO SPECT images of low contrast in affected and unaffected area.

Decreased perfusion in the bilateral parietal regions was an important finding, because it is useful in differentiating between Alzheimer's disease and MID.[10,12] Decreased CMRGlc in the bilateral frontal regions was reported by FDG PET in a proven case with Pick's disease.[8] IMP and HMPAO SPECT studies could detect these patterns, and thought to be useful in the differential diagnosis of dementia.

In this study, we compared SPECT with PET by using semiquantative methods, because quantification was not performed in SPECT studies. As our patients showed global decrease in CBF or CMRGlc, quantification may be useful in the study of dementia. Quantification is an important aspect of the SPECT studies and further studies on the quantitative validation of SPECT studies in the detection of early changes in cerebral hemodynamics are needed.

As mentioned above, IMP and HMPAO SPECT studies can be used in the detection of abnormal regions in dementia and are useful in the differential diagnosis of dementia though they have some limitations compared with PET studies.

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