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Cerebral blood flow, oxygen and glucose metabolism with PET in progressive supranuclear palsy

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Cerebral blood flow, cerebral oxygen metabolic rate and cerebral glucose metabolic rate were measured with positron emission tomography (PET) in four patients with progressive supranuclear palsy (PSP). Decreased blood flow and hypometabolism of oxygen and glucose were found in both subcortical and cortical regions, particularly in the striatum including the head of the caudate nucleus and the frontal cortex. The coupling between blood flow and metabolism was preserved even in the regions which showed decreased blood flow and hypometabolism. These findings indicated the hypofunction, as revealed by decreased blood flow and hypometabolism on PET, both in the striatum and the frontal cortex, and which may underlie the pathophysiological mechanism of motor and mental disturbance in PSP.

Key words: Progressive supranuclear palsy, Subcortical dementia, Positron emission tomography

INTRODUCTION

PROGRESSIVE SUPRANUCLEAR PALSY (PSP) is characterized clinically by impaired ocular motility, pseudobulbar palsy, axial dystonia and dementia. Dementia associated with PSP has been considered to be subcortical dementia, since the neuropathological lesions are located only in the subcortical structures and usually little pathological involvement is seen in the cortical regions.[1,2] The dementia in PSP has clinical features such as (a) forgetfulness, (b) slowing of thought process and (c) impaired ability to manipulate acquired knowledge[3] and the intellectual impairment is rather mild in PSP when compared with cortical dementias such as Alzheimer's disease or Pick's disease.[4] Frontal dysfunction might manifest clinical features of dementia in PSP,[3,4] however, the underlying pathophysiological mechanism has not been fully elucidated.

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Positron emission tomography (PET) has disclosed physiological changes in several kinds of brain disorders. As for dementia, many studies have been done on Alzheimer's disease,[5–10] but only a few reports are available on PSP because of the very low incidence of the disease. Recently D'Antona et al. showed that the cortical glucose metabolic rate measured with PET in patients with PSP was clearly decreased especially in the frontal cortex.[11] Leenders et al. also reported a global decrease in cerebral blood flow and oxygen utilization, particularly in the frontal region and a significant decrease in L-(^{18}F) fluorodopa uptake in the striatum compared with the control.[12] In the present paper, we studied the cerebral circulation and metabolism, using three different parameters, cerebral blood flow, and oxygen and glucose metabolism both in the cortical and subcortical regions in patients with PSP in order to clarify the regional cerebral dysfunction in PSP.

MATERIALS AND METHODS

Patients

Four patients diagnosed clinically as PSP were

Table 1 Clinical features of four patients with PSP

Case No.	Age/Sex	Disease duration	Ocular motility	Neck dystonia	Gait disturbance	Pseudobulbar palsy	Cognitive impairment	Loss of initiation	Behavioural changes
1	71/M	4 (yrs)	Vertical gaze palsy	++	−	++	+	+	−
2	44/M	2	Vertical gaze palsy	−	+	+	+	+	−
3	49/F	2	Vertical gaze palsy	−	+	+	+	+	+
4	66/F	10	Down gaze palsy	+	+	−	++	+	++

++: moderate +: mild −: no change

studied (Table 1). The regional cerebral blood flow (rCBF), regional cerebral metabolic rate of oxygen ($rCMRO_2$) and regional oxygen extraction fraction (rOEF) were measured in cases 1 and 2, and the regional cerebral metabolic rate of glucose (rCMRGlc) was measured in cases 2, 3 and 4.

Case 1. A 71-yr-old man had started to complain of visual disturbance at the age of 67. This was followed by progressive difficulty in walking, reduction in voice volume and slurred speech. Later, difficulty in swallowing was also noted. On examination vertical gaze palsy, pseudobulbar palsy, neck dystonia, rigidity of the lower extremities, and general slowness of movement were found. His calculating skills were impaired but memory was almost normal.

Case 2. A 44-yr-old man had started to complain of tremor of both hands at the age of 42. This was followed by progressive slowness, difficulty in walking and writing and visual disturbance. Later, difficulty in swallowing and speaking and forgetfulness were noted. On examination he showed vertical gaze palsy, pseudobulbar palsy, neck dystonia and hyperreflexia of the upper and lower extremities. He had mild memory disturbance.

Case 3. A 49-yr-old woman had started to complain of visual disturbance at the age of 47. This was followed by bradykinesia and a tendency to fall. Later, difficulty in swallowing, slow speaking and forgetfulness were noted. Abnormal behaviour due to hallucination was also noted. On examination she showed vertical gaze palsy, pseudobulbar palsy, neck dystonia and hyperreflexia of the upper and lower extremities. She had mild memory disturbance.

Case 4. A 66-yr-old woman started to complain of a tremor in the right foot at the age of 56. At the age of 60, bradykinesia and a tendency to fall appeared. Later, forgetfulness and abnormal behaviour due to hallucination was noted. On examination, she showed down gaze palsy, neck rigidity and mild rigidity of the extremities. Her memory and calculating skills were impaired. Slow cognition was noted.

For comparison five age-matched subjects without known brain disorders or intellectual impairment underwent rCMRGlc studies, and the four other normal volunteers had rCBF, $rCMRO_2$ and rOEF studies performed.

Methods

Positron emission tomography was performed with a HEADTOME III (Shimadzu Corp., Japan) at a spacial resolution of 8.2 mm full width at half maximum (FWHM).[13] Five slices were obtained in a single scanning. The oxygen-15 steady state technique was used to measure rCBF, $rCMRO_2$ and rOEF.[14] Continuous injection of 100 mCi (3.7 GBq) of oxygen-15 labeled water and continuous inhalation of 100 mCi (3.7 GBq) of oxygen-15 gas were employed. Arterial blood sampling was performed three or four times during each emission scan. Regional $CMRO_2$ was corrected with the rCBV value which was measured with a single inhalation of 50 mCi (1.85 GBq) of oxygen-15 labeled carbon monoxide.[15,16] Regional CMRGlc was measured on a different day using fluorine-18 fluoro-2-deoxy-D-glucose (^{18}F-FDG). A bolus of 3 to 7 mCi (111 to 259 MBq) of ^{18}F-FDG was injected intravenously, and arterial blood samples were obtained from a catheter in the femoral artery at predetermined intervals from the time of injection until the end of scanning. Regional CMRGlc was determined from the emission scan and blood curve data by using the model of Sokoloff et al.[17] and later modified by Hutchins et al.[18] A transmission scan with a ^{68}Ge/^{68}Ga ring source was obtained for correction of attenuation. Five slices were taken in the orbitomeatal line (OM) +2 cm, +3.5 cm, +5 cm, +6.5 cm and +8 cm planes by a single scanning.

Regional profile measurements were obtained in square, rectangular or teardrop-shaped regions of interest (ROI's) sited anatomically (Fig. 1). Two regions were sited in the OM +2 cm plane (cerebellar hemisphere and brain stem), two were located in the OM +3.5 cm plane (temporal and hippocampus). A further five were in the OM +5 cm

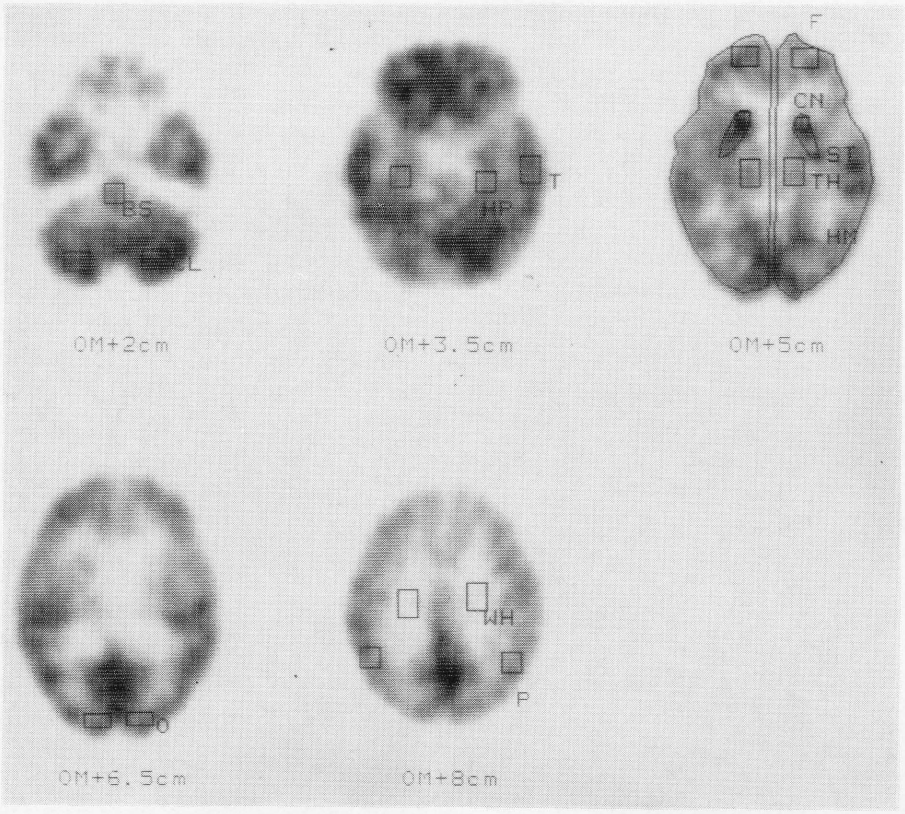
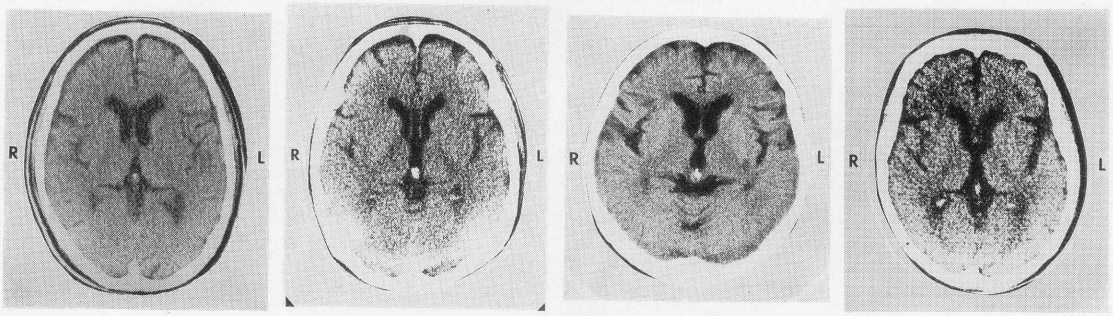


Fig. 1 Regions of interest in PET images. The regions of cerebellar hemisphere (CL) and brain stem (BS) were sited in the OM+2 cm plane, the regions of temporal (T) and hippocampus (HP) were sited in the OM+3.5 cm plane, the regions of frontal (F), caudate nucleus (CN), striatum (ST), thalamus (TH), and global cerebral hemisphere (HM) were sited in the OM+5 cm plane, the regions of occipital (O) were sited in the OM+6.5 cm plane and the regions of parietal (P) and white matter (WH) sited in the OM+8 cm plane.



a b c d

Fig. 2 The CT images at the level of striatum of cases 1 (a), 2(b), 3(c) and 4(d). The CT of all four cases show mild cerebral atrophy without any localized lesions.

plane (frontal, head of the caudate nucleus, striatum, thalamus and global cerebral hemisphere), one was in the OM +6.5 cm plane (occipital) and two were in the OM +8 cm plane (parietal and white matter of the centrum semiovale). The region of the thalamus was sited in the OM +6.5 cm plane instead of in the OM +5 cm plane in some subjects in order to avoid a partial volume effect. To study the correlation between rCBF and the metabolism of each region in PSP patients, altogether 47 ROI's (including the 19 ROI's described above except for two ROI's of the global cerebral hemisphere) were taken in each patient. The correlation between rCBF and $rCMRO_2$ was studied with ROI's in cases 1 and 2, and the correlation between rCBF and rCMRGlc was studied with ROI's in case 2.

Regional values for CBF, $CMRO_2$, OEF and CMRGlc in PSP patients were compared with the mean values for the controls. Since no significant asymmetry was observed except for the thalamus of case 1, values were calculated as the mean of the bilateral sides. Individual values for the right side and left side were shown only in the thalamus of case 1.

RESULTS

The CT of all four patients with PSP showed mild cortical atrophy without any localized lesions (Fig. 2). The PET images showed a decrease in rCBF, $rCMRO_2$ and rCMRGlc in the subcortical regions and in the frontal cortex compared with normal controls (Fig. 3).

Regional values for CBF, $CMRO_2$, OEF and CMRGlc are shown in Tables 2a to 2d, respectively. Decreased rCBF was observed in the frontal cortex, striatum including the head of the caudate nucleus and the cerebral hemisphere in cases 1 and 2, and decreased rCBF was also observed in the left thalamus and white matter of case 1, and in the cerebellar hemisphere of case 2 compared with the mean values for four controls (Table 2a). Regional $CMRO_2$

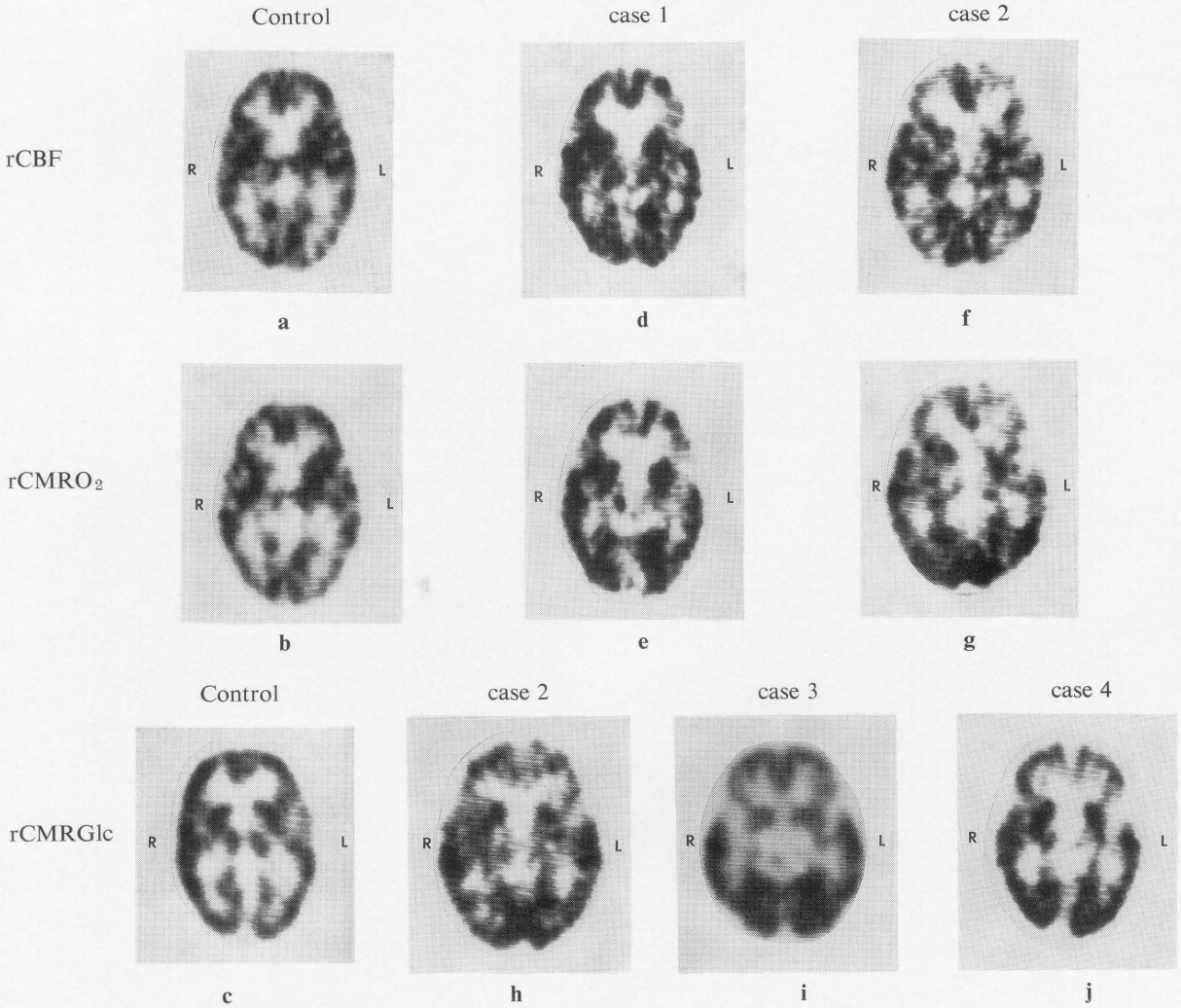


Fig. 3 The PET images, at the level of striatum (OM+5 cm), representing rCBF (a), $rCMRO_2$ (b) and rCMRGlc (c) of normal controls, rCBF (d) and $rCMRO_2$ (e) of case 1, rCBF (f), $rCMRO_2$ (g) and rCMRGlc (h) of case 2 and rCMRGlc (i, j) of cases 3 and 4, respectively. In case 1, rCBF image shows slight decrease in frontal cortex (d) and $rCMRO_2$ image shows decrease in frontal cortex and the left thalamus (e). All three kinds of images in case 2 show decrease in frontal cortex and striatum including caudate nucleus (f, g, h). In case 3, rCMRGlc image shows decrease in frontal cortex and striatum including caudate nucleus (i). In case 4, rCMRGlc image shows decrease in frontal cortex and seems to show decrease in left thalamus (j), but there was no decrease in value of rCMRGlc in left thalamus.

Table 2a Regional CBF values† in two PSP cases compared with mean values for four controls (ml/100 ml/min)

Region	Case 1	Case 2	Controls (mean±SD)
Cerebellum	32.1	27.9*	49.1±8.7
Brain stem	25.1	25.0	34.0±5.2
Cortex			
frontal	24.3*	23.2*	35.9±4.8
temporal	24.9	24.9	35.2±5.7
parietal	26.0	31.3	36.6±6.2
occipital	24.4	25.9	32.1±3.9
hippocampus	24.8	25.5	35.7±5.7
Subcortex			
striatum	27.1*	28.9*	46.7±7.1
caudate n.	22.4*	26.3*	47.6±8.9
thalamus	26.3	28.3	39.4±6.7
	(Lt 24.6* Rt 27.9)		
White matter	9.7*	10.5	17.1±3.5
Hemisphere	23.8*	25.8*	36.7±4.6

†Values represent the mean for the bilateral sides except for the thalamus in case 1.
*Decreased values more than 2 standard deviations from the mean control values.

Table 2b Regional $CMRO_2$ values† in two PSP cases compared with mean values for four controls (ml/100 ml/min)

Region	Case 1	Case 2	Controls (mean±SD)
Cerebellum	2.48*	2.70	3.24±0.32
Brain stem	1.31	1.57	1.86±0.33
Cortex			
frontal	1.92*	2.02*	2.77±0.37
temporal	2.03	2.28	2.55±0.28
parietal	2.04	2.92	2.82±0.39
occipital	2.13	2.55	2.59±0.48
hippocampus	1.96	1.92	2.24±0.35
Subcortex			
striatum	2.11*	2.57*	3.40±0.41
caudate n.	1.69*	2.49*	3.10±0.30
thalamus	1.73	2.03	2.53±0.41
	(Lt 1.55* Rt 1.91)		
White matter	0.64*	0.80	1.13±0.18
Hemisphere	1.82*	2.26	2.62±0.25

†Values represent the mean for the bilateral sides except for the thalamus in case 1.
*Decreased values more than 2 standard deviations from the mean control values.

decreased in the cerebellum, white matter, cerebral hemisphere and left thalamus of case 1, and in the frontal cortex and striatum including the caudate nucleus of cases 1 and 2 compared with the mean values for four controls (Table 2b). Regional OEF did not increase or decrease (Table 2c). Regional CMRGlc decreased in the cerebellum and the temporal cortex in case 2, in the parietal cortex in case 3, in the white matter in case 4 and in the frontal cortex, striatum including the caudate nucleus and cerebral hemisphere in cases 2, 3 and 4 compared with the mean values for five controls (Table 2d). There was no significant difference in rCMRGlc in the left

Table 2c Regional OEF values† in two PSP cases compared with mean values for four controls (%)

Region	Case 1	Case 2	Controls (mean±SD)
Cerebellum	43.4	46.9	34.3±6.3
Brain stem	37.7	30.5	28.3±7.1
Cortex			
frontal	43.9	42.0	39.3±6.8
temporal	45.6	44.2	37.6±7.8
parietal	44.5	45.0	39.9±7.4
occipital	48.9	47.6	39.4±6.7
hippocampus	39.5	36.4	31.4±7.5
Subcortex			
striatum	43.1	43.2	37.1±11.1
caudate n.	40.6	46.0	36.0±7.2
thalamus	37.3	35.0	35.2±6.5
	(Lt 35.8 Rt 38.8)		
White matter	38.8	36.9	34.5±7.9
Hemisphere	42.8	42.5	37.2±6.0

†Values represent the mean for the bilateral sides except for the thalamus in case 1.

Table 2d Regional CMRGlc values† in three PSP cases compared with mean values for five controls (mg/100 ml/min)

Region	Case 2	Case 3	Case 4	Controls (mean±SD)
Cerebellum	5.20*	5.64	6.90	6.78±0.77
Brain stem	4.36	4.59	4.85	5.27±0.64
Cortex				
frontal	5.21*	4.83*	5.63*	7.19±0.35
temporal	5.19*	5.59	6.31	6.84±0.68
parietal	6.71	5.64*	7.01	7.43±0.43
occipital	5.25	5.64	6.85	6.75±0.59
hippocampus	4.74	4.33*	4.86	5.54±0.51
Subcortex				
striatum	5.93*	5.57*	5.66*	7.56±0.34
caudate n.	6.31*	5.39*	4.28*	7.29±0.17
thalamus	4.84	4.83	5.27	6.70±1.00
White matter	3.00	3.54	2.51*	3.81±0.50
Hemisphere	5.01*	4.87*	5.20*	6.52±0.43

†Values represent the mean for the bilateral sides.
*Decreased values more than 2 standard deviations from the mean control values.

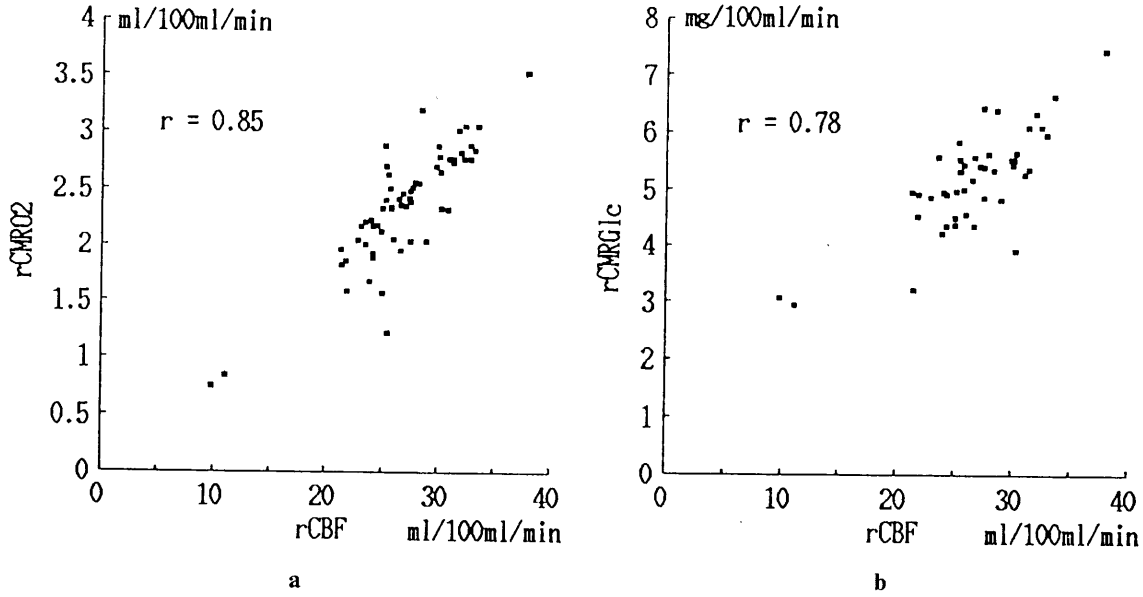


Fig. 4 Correlation between rCBF and $rCMRO_2$ in cases 1 and 2 (a), and correlation between rCBF and rCMRGlc in case 2 (b). The correlation coefficients between rCBF and $rCMRO_2$, and between rCBF and rCMRGlc were 0.85 and 0.78, respectively.

thalamus (5.25 mg/100 ml/min) and right thalamus (5.29 mg/100 ml/min) in case 4, although the rCMRGlc image seemed to decrease in the left thalamus (Fig. 3j).

The correlation between rCBF and $rCMRO_2$ in cases 1 and 2 is shown in Fig. 4a, and the correlation between rCBF and rCMRGlc in case 2 is shown in Fig. 4b. The correlation coefficients for rCBF and $rCMRO_2$, and for rCBF and rCMRGlc were 0.85 and 0.78, respectively. There were fairly good correlations between rCBF and $rCMRO_2$ and between rCBF and rCMRGlc in the patients with PSP.

DISCUSSION

In spite of minimum morphological alterations seen in CT, the PET study in patients with PSP showed significantly decreased blood flow and hypometabolism in both the subcortical and cortical regions particularly in the striatum including the head of the caudate nucleus and the frontal cortex, which might underlie the pathophysiological mechanism of PSP. Neuropathological studies have shown that PSP is characterized by neuronal loss, accentuation of Alzheimer's neurofibrillary tangles (ANT) and gliosis affecting several subcortical structures, but with relative sparing of the cerebral cortex.[1,3,4,19] Many investigators have reported that ANT is absent or very rare in the cerebral cortex of PSP patients.[20–22] On the other hand, Ishino et al. found ANT in the cerebral cortex especially in the hippocampus and it was postulated that the occurrence of ANT in the cerebral cortex was one of the morphological manifestations of PSP.[23] In our PET study, we found decreased blood flow and hypometabolism in the striatum which is involved pathologically, and in the frontal cortex which seems to be little affected pathologically, but no change was observed in the hippocampus (Table 2). It is unlikely that the morphological changes cause decreased blood flow or hypometabolism in the frontal cortex. Instead, impaired neuronal input from the histologically involved subcortical regions such as the striatum, which is known to have abundant neuronal connections with the frontal cortex, might cause hypofunction in the frontal cortex,[11] and which results in decreased blood flow and hypometabolism. Main pathological changes are in the basal ganglia and brain stem, but in this study no definite decreased blood flow or hypometabolism was observed in the brain stem. The volume may be affected somewhat in the brain stem because not every part of brain stem was considered to be involved in the disease. Hence, it is likely that both pathological involvement of the disease and the loss of neuronal input from the structures involved cause the decreased blood flow and hypometabolism in PSP patients.

It is known that there is a close correlation between blood flow and metabolism in the normal brain.[17,24] In PSP patients, from the rCBF and $rCMRO_2$ data reported by Leenders et al. there seemed to be a good correlation between rCBF and $rCMRO_2$.[12] In this study, three different parameters, cerebral blood flow, oxygen and glucose utilization

were examined and it was revealed that there was a good correlation not only between rCBF and $rCMRO_2$ but also between rCBF and rCMRGlc in the patients with PSP. Leenders et al. mentioned that blood flow was impaired to a greater extent than oxygen utilization, resulting in increased rOEF,[12] however, our rOEF values were neither increased nor decreased in patients with PSP. The $PaCO_2$ levels may indicate this. $PaCO_2$ values in their study were 36.6 ± 2.9 for patients and 42.0 ± 1.4 for controls, and in this study they were 38.9 ± 0.8 for patients and 42.9 ± 4.7 for controls, respectively. In the other PET study with carbon dioxide loading, the rate of blood flow increase was almost five percent for every mmHg increase in $PaCO_2$ (Otsuka et al. in preparation). A coupling between blood flow and metabolism in PSP patients is understandable, because PSP is a chronic degenerative disease.

PET findings on cerebral blood flow and metabolism in PSP are apparently different from those of cortical dementia. In Alzheimer's disease, glucose metabolism was found to be decreased in the association area of the temporoparietal region.[9] In frontal non-Alzheimer dementia including Pick's disease, hypometabolism of glucose in the bilateral frontal region,[25] especially in the medial frontal region, was characteristic.[26] It should be remembered that the hypometabolic cortical regions in cortical dementia accompanied pathological changes, whereas there was little pathological involvement of the hypometabolic frontal cortex in PSP.

To conclude, the present study disclosed the hypofunction in both cortical and subcortical regions, particularly in the striatum including the head of the caudate nucleus and in the frontal cortex in view of three different parameters, i.e. blood flow, oxygen and glucose metabolism, which may underlie the pathophysiological mechanism of dementia and motor disturbance in PSP.

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