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Regional cerebral glucose metabolism in patients with Parkinson's disease with or without dementia

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By means of positron emission tomography, the cerebral glucose metabolism in 5 patients with Parkinson's disease with dementia was compared with that in 9 patients without dementia, and that in 5 normal volunteers. The metabolic rates for glucose were measured by placing one hundred regions of interest. In the demented patients, cerebral glucose metabolism was diffusely decreased compared with that of the non-demented patients and the normal controls. The most significant decrease in glucose metabolism was observed in the angular gyrus (49.7% of the normal controls). The glucose metabolism in the cingulate, pre- and postcentral, occipital and subcortical regions was relatively spared (62.1 to 85.5% of the normal controls). In the patients without dementia, the glucose metabolism in each region was not significantly different from that in the normal controls. These results suggest that diffuse glucose hypometabolism in the cerebral cortex may correlate with that of patients with Parkinson's disease with dementia.

Key words: positron emission tomography, fluorodeoxyglucose, glucose metabolism, Parkinson's disease, dementia

INTRODUCTION

PARKINSON'S DISEASE is a disease entity characterized by extrapyramidal symptoms including a resting tremor, hypokinesia and rigidity. However, recent reports have revealed that approximately one third of patients with Parkinson's disease will develop dementia.[1,2] The clinical features of the dementia of Parkinson's disease are similar to those of progressive supranuclear palsy and Huntington's chorea. Their dementia is termed "subcortical dementia" and is differentiated from the cortical dementia representative of Alzheimer's disease.[3] In demented patients with Parkinson's disease, cerebral glucose metabolism measured by positron emission tomography is reported to be diffusely decreased in the cerebral cortex.[4,5]

In the present study, we examined the cerebral glucose metabolism in demented patients with Parkinson's disease, and calculated the metabolic rate for glucose in each small region by placing one hundred regions of interest. We compared them with those in non-demented patients with Parkinson's disease and with those in normal controls, to determine whether there are specific regions of cerebral glucose hypometabolism.

MATERIALS AND METHODS

Patients

Fourteen patients with Parkinson's disease were examined (Table 1). All patients except one (Case 2) had three classic signs of resting tremor, rigidity and akinesia, without pyramidal signs and with good response to levodopa. The severity of their disease

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was evaluated and classified in stages I, II, III and IV along with their level of functional disability according to Hoehn and Yahr.[6] Five patients were demented (PDD); 9 were not (PD), on the basis of neuropsychological evaluation according to Hasegawa's Dementia Scale.[7] X-ray computed tomography (XCT) and/or magnetic resonance imaging (MRI) were performed to exclude organic diseases, especially cerebro-vascular diseases. They were also used for the evaluation of cerebral atrophy. The degree of central sulcal widening, an estimation of cortical atrophy, was graded as follows: none, mild (3 mm or less), moderate (4 to 5 mm) and marked (more than 5 mm). Case 2, who had no tremor, was clinically diagnosed as Parkinson's disease, because of the long duration, gradual progression and the effectiveness of levodopa. Before the PET studies were performed, none of the patients received drugs for at least 72 hours.

The mean age of the PDD group was 62 yrs (range 56–65 years); that of the PD group was 50.7 yrs (range 37–67 years). The difference between these two groups in the mean age was statistically significant. The clinical stage of the PDD group was III or IV and that of the PD group was I or III. According to the Hasegawa's Dementia Scale, the scores in the PDD patients were lower than 20.0 points and those in the PD patients were 32.5 points. By XCT and/or MRI, mild cortical atrophy was revealed in Case 2, 3, 4 and 5.

Five normal female vounteers were also examined for comparison. They were age-matched with the PDD patients and their mean age was 61.5 yrs (range 51–66 years). None of the volunteers had neurological or neuropsychological abnormalities. The absence of organic disorders in them was confirmed by XCT.

PET system

We used the ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) method to measure the regional cerebral metabolic rate for glucose (rCMRGlc). Fluorine-18 was produced in a cyclotron BC1710 (The Japan Steel Works Corp.) by the ^{20}Ne(d,a)^{18}F reaction, and FDG was synthesized by the method reported by Biada et al.[8] PET was performed with a HEADTOME III (Shimadzu Corporation, Japan) at a spatial resolution of 8.2 mm full width at half maximum (FWHM).[9] A transmission scan with a ^{68}Ge/^{68}Ga ring source was obtained for the correction of attenuation. Five contiguous slices were obtained in the orbitomeatal line (OM) +20 mm, +35 mm, +50 mm, +65 mm and +80 mm planes. Two to eight mCi (74 to 296 MBq) of ^{18}F-FDG were administered intravenously, and arterial blood samples were obtained at predetermined intervals from the time of injection until the end of scanning. The rCMRGlc (mg/min/100 m*l*) was determined from the emission scan (eight minutes scan from commencing 63 minutes after injection), and blood curve data using the model of Phelps et al.,[10] later modified by Brooks.[11] Literature value for the lumped constant of 0.42 was employed.[10]

One hundred regions of interest (ROIs) were placed in 22 regions by manual tracing (Fig. 1). Individual regions were combined into anatomical and functional combinations guided by CT and/or MRI, and an atlas of axial tomographic anatomy. The rCMRGlc values were obtained for cortical areas corresponding to the superior frontal (SF), middle frontal (MF), inferior frontal (IF), cingulate (Ci), precentral (Pre), superior temporal (ST), middle temporal (MT), inferior temporal (IT), postcentral (Post), angular (AG), supramarginal (SM), occipital regions (OC) and cuneus (Cu), for sub-

Table 1 Clinical features of patients with Parkinson's disease with or without dementia

	With dementia					Without dementia								
Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age	56	65	65	64	60	37	41	52	47	56	67	53	50	53
Sex	F	M	M	M	M	F	M	M	M	F	F	F	F	M
Duration (years)	10	18	8	10	3	5	2	4	1	2	7	6	6	7
Clinical Stage*	III	III	III	III	IV	I	I	I	III	III	III	III	III	III
Tremor	+	−	+	+	+	+	++	++	+	+	++	+	+	+
Rigidity	+++	++	++	++	++	+	+	++	++	++	++	++	++	+
Akinesia	++	++	++	++	++	+	+	+	++	++	+	++	++	++
Pyramidal sign	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Efficacy of L-DOPA	+	+	+	−	+	+	+	+	+	+	+	+	+	+
HDS**	11.5	20.0	18.0	19.0	17.0	32.5	32.5	32.5	32.5	32.5	32.5	32.5	32.5	32.5
Cerebral atrophy***														
sulcal widening	−	+	+	+	+	−	−	−	−	−	−	−	−	−

*: Hoehn and Yahr classification, **: Hasegawa's Dementia Scale, ***: defined by XCT and/or MRI, (−): none, (+): mild (3 mm or less).

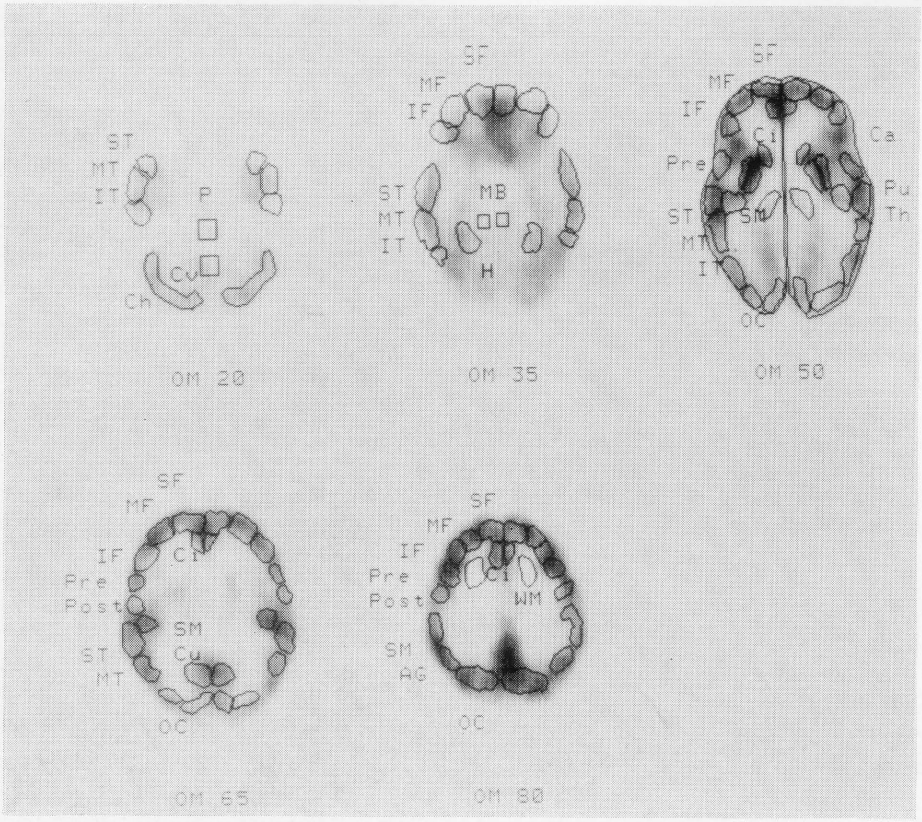

Fig. 1 Regions of interest (ROIs). One hundred regions of interest were placed in appropriate regions in 5 contiguous displayed slices. Slices were obtained in the orbitomeatal (OM) line +20, +35, +50, +65 and +80 mm planes. ROIs were placed in the superior frontal (SF), middle frontal (MF), inferior frontal (IF), cingulate (Ci), precentral (Pre), superior temporal (ST), middle temporal (MT), inferior temporal (IT), postcentral (Post), angular (AG), supramarginal (SM), occipital regions (OC) and cuneus (Cu), for subcortical areas corresponding to the caudate nucleus (Ca), putamen (Pu), thalamus (Th), hippocampus (H) and white matter (WM). ROIs of the midbrain (MB), pons (P), cerebellar hemisphere (Ch) and cerebellar vermis (Cv) were also placed. The regions of interest for the global cerebral hemisphere were placed at the slice level OM+50 mm.

cortical areas corresponding to the caudate nucleus (Ca), putamen (Pu), thalamus (Th), hippocampus (H) and white matter (WM). The rCMRGlc values for the midbrain (MB), pons (P), cerebellar hemisphere (Ch) and cerebellar vermis (Cv) were also obtained. All ROIs consisted of 11–137 mm^2. The regions of interest for the global cerebral hemisphere were placed in the slice level OM +50 mm. The rCMRGlc values for the left and the right regions were averaged and used for the rCMRGlc of each region. Statistical analysis for intergroup comparisons of the rCMRGlc were made by Student's t test.

RESULTS

The rCMRGlc for each region in the normal controls, the PD group and the PDD group are presented in Table 2. In the PDD group, the rCMRGlc values were decreased in all regions compared with those in both the PD group and the normal controls. In contrast, the rCMRGlc values for all regions in the PD group were not significantly different from those in the normal controls.

The rCMRGlc in the cerebral cortices in the PDD group were diffusely decreased; their values were 3.8–5.61 mg/min/100 m*l*. The most significant decrease in the rCMRGlc was observed in the angular gyrus; its value was 3.8 mg/min/100 m*l*. There was no significant difference between sides (data not shown). The rCMRGlc in the cingulate gyrus, precentral area, postcentral area, cuneus and occipital lobe were decreased and the decrease was statistically significant, but the decrease was not as great as that in the other cerebral cortices.

In the subcortical regions in the PDD group, the decreases in the rCMRGlc in the caudate nucleus, putamen, thalamus and hippocampus were signifi-

Table 2 The regional cerebral metabolic rates for glucose by region

	Normal (n=5)	PD[a] (n=9)	PDD[b] (n=5)
Cerebral hemisphere	6.32±0.45	6.32±0.57	4.31±0.51[c,d]
Cerebral white matter	4.68±0.74	4.38±0.85	3.08±0.57[c]
Frontal cortex			
Cingulate	7.41±0.63	7.43±1.02	4.92±0.83[c,d]
Superior frontal	7.48±0.51	7.06±1.00	4.41±0.68[c,d]
Middle frontal	7.71±0.61	7.62±0.97	4.53±0.72[c,d]
Inferior frontal	7.68±0.70	7.48±0.94	4.47±0.81[c,d]
Precentral	7.42±0.65	7.27±0.74	4.85±0.90[c,d]
Parietal cortex			
Postcentral	7.16±0.78	6.91±0.70	5.23±1.10
Supramarginal	7.41±0.74	7.40±1.00	4.72±0.86[c,d]
Angular	7.64±0.63	7.44±1.04	3.80±0.38[c,d]
Temporal cortex			
Superior temporal	7.25±0.82	7.23±0.91	4.27±0.73[c,d]
Middle temporal	7.43±0.83	7.26±0.92	4.37±0.75[c,d]
Inferior temporal	6.99±0.79	6.80±0.85	4.18±0.65[c,d]
Occipital cortex			
Occipital	7.13±0.88	6.61±0.85	4.43±0.56[c,d]
Cuneus	8.20±1.12	8.24±1.07	5.61±0.72[c,d]
Subcortical			
Caudate	7.03±0.29	7.50±0.73	5.85±0.62[c,d]
Puntamen	7.86±0.34	8.33±0.77	6.57±0.61[c,d]
Thalamus	6.56±1.11	7.10±0.65	5.61±0.98[d]
Hippocampus	6.07±0.59	6.27±0.67	4.42±0.54[c,d]
Cerebellar cortex	6.35±0.51	7.07±0.64	5.22±0.53[d]
Cerebellar vermis	6.01±0.68	6.46±0.61	5.40±0.58
Pons	5.20±0.74	5.27±0.36	4.42±0.75
Midbrain	5.15±0.55	5.40±0.59	4.41±0.49

mean±SD mg/min/100 m*l*, [a] Parkinson's disease without dementia, [b] Parkinson's disease with dementia, [c] rCMRGlc in PDD group<Normal volunteers, $p<0.01$, [d] rCMRGlc in PDD group<PD group, $p<0.01$.

cant, but relatively mild compared with those in the cerebral cortices. The rCMRGlc values for the cerebellar hemisphere, cerebellar vermis, pons and midbrain in the PDD group were 4.41–5.40 mg/min/100 m*l*. The decreases among them were not statistically significant. However, the rCMRGlc values for the thalamus and cerebellar hemisphere were significantly lower in the PDD group than those in the PD group.

The PET images of the PDD (Fig. 2, lower row) show diffuse hypometabolism in the cerebral cortex and relatively preserved pre- and postcentral, occipital regions, striatum, thalamus and cerebellum, in contrast to the normal rCMRGlc pattern of the PD (Fig. 2, upper row).

DISCUSSION

The predominant pathology of Parkinson's disease is the degeneration of dopaminergic neurons within the substantia nigra. In demented patients with Parkinson's disease, three types of cortical pathologic changes have been suggested. The first is a brain stem type of Lewy body disease without any change in the cerebral cortex.[12] The second type includes neurofibrillary tangles, neuritic plaques and neuronal cell loss which are similar to those seen in Alzheimer's disease.[13] The third type is a diffuse Lewy body disease in which both multiple Lewy body and Alzheimer-like pathologic changes can be observed in the cerebral cortex.[14] It is well known that the pattern of cerebral glucose metabolism measured by positron emission tomography is associated with pathologic changes in several disorders, as seen in Alzheimer's disease demonstrating predominant hypometabolism in the temporo-parietal cortex.[15]

Concerning the rCMRGlc in the PDD, several reports have described decreased glucose metabolism in the cerebral cortices. Kuhl et al. first demonstrated uniformly reduced cerebral glucose metabolism in one demented patient.[4] They observed severe parietal hypometabolism similar to that seen in Alzheimer's disease. Okada et al. examined seven demented patients and demonstrated diffuse hypometabolism in the cerebral cortex.[16] In these reports, the rCMRGlc in cortical lobes was represented by a small ROI placed in one part of each lobe. However, to determine whether there are specific regions of hypo-

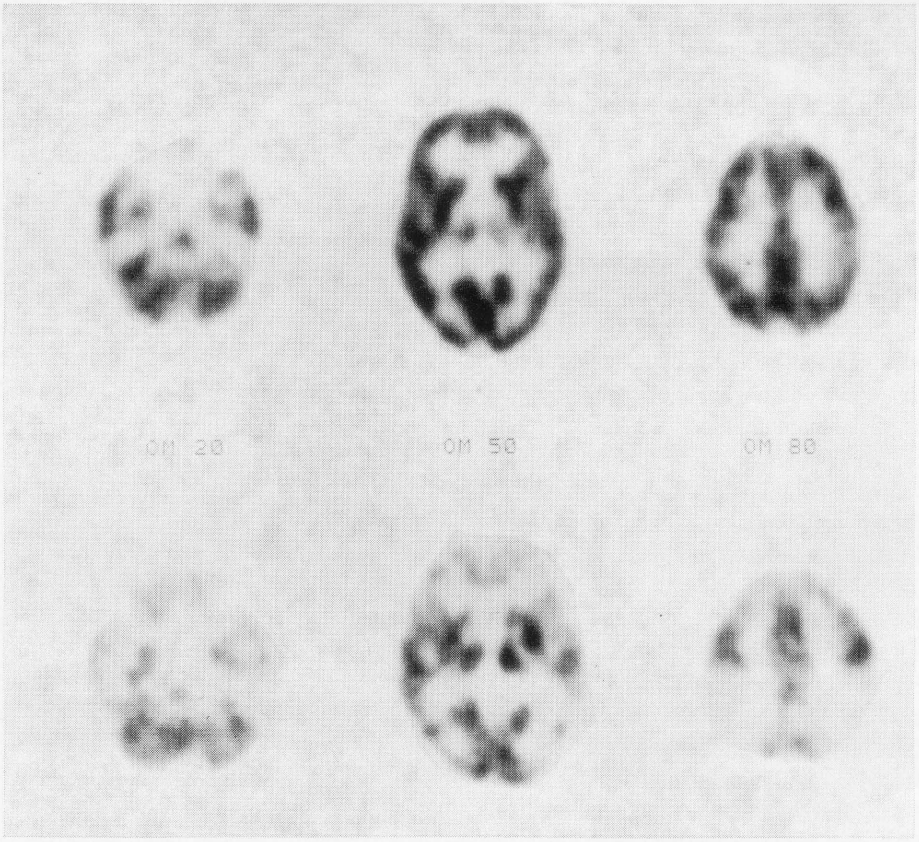

Fig. 2 A comparison of PET images, at levels OM +20 mm, OM +50 mm and OM +80 mm, representing rCMRGlc from non-demented patients with Parkinson's disease (Case 6) (upper three images) and demented patients with Parkinson's disease (Case 5) (lower three images). The images of a non-demented patient show no abnormalities. In contrast, the images of a demented patient show diffuse hypometabolism of the cerebral cortex and relatively preserved pre- and postcentral, occipital regions, striatum, thalamus and cerebellum.

metabolism in dementia, glucose metabolism should be measured in numerous small regions. To analyze the pattern of cerebral glucose metabolism, Peppard et al. placed multiple rectangular ROIs along the cerebral cortex and reported observing similar patterns of cortical hypometabolism in both Alzheimer's disease and Parkinson's disease with dementia.[5] We examined the cerebral glucose metabolism of the PDD by placing one hundred ROIs, and by tracing every small region, guided by CT and/or MRI, and using an atlas, although it was difficult to identify each gyrus on the PET images because of the limited resolution of our PET scanner.

In the present study the rCMRGlc value in the PD group was not significantly different from that in the normal controls in all regions. The rCMRGlc in the caudate nucleus and the putamen were slightly higher than those in the normal controls, but they were not statistically significant.

In the PDD group, our results demonstrated diffuse hypometabolism in the cerebral cortex and this was consistent with previous reports.[4,16] As mentioned in materials, the mean age of the PDD group was higher than that of the PD group, and the rCMRGlc may decrease with age. However, as our normal controls were age-matched with the PDD group, the decrease in rCMRGlc in the PDD group can not be explained only by the PDD and the PD group age difference. The most significant decrease in rCMRGlc was observed in the angular gyrus. Decreased rCMRGlc in the angular gyrus in the PDD group was also observed by Peppard et al.[5] They also suggested that the cortical dysfunction of the PDD has a similar pattern to that of Alzheimer's disease as determined by Q-component analysis.[17] We did not analyze the rCMRGlc pattern statistically, but the PET images suggested a similarity between the PDD and Alzheimer's disease (Fig. 2). The neuropsychological dysfunction of the PDD group is suggested to have a relationship with the hypometabolism of the angular gyrus, one of association neocortices, as in Alzheimer's disease. In other association neocortices, the rCMRGlc values for the frontal and temporal cortices were also

decreased. It is suggested that cortical pathologic changes in PDD may be classified into three types. It is possible that the three types of PDD have different glucose metabolism patterns. We could not classify our 5 PDD patients into three pathologic types, because their pathologic features have not been verified. Further examinations should be performed to determine whether the glucose metabolism of these types is different.

In the PDD group, the rCMRGlc values for the cingulate gyrus, precentral area, postcentral area, cuneus and occipital lobe were not greatly decreased compared with other cerebral cortices. Peppard et al. also demonstrated decreased rCMRGlc in the left perirolandic area.[5] In our study, the rCMRGlc values for the right and left precentral areas in the PDD group were 4.93 and 4.77 mg/min/100 m*l*, respectively. In the postcentral areas, they were 5.31 mg/min/100 m*l* on the right side and 5.14 mg/min/100 m*l* on the left side. These values were apparently lower than those in the normal controls, but they were relatively spared (64.3 to 74.2% of normal controls) in comparison with the other cerebral cortices. Furthermore, there were no significant differences between sides in the pre- and postcentral areas. The reason for the differences between our data and those of the previous study is not clear.

When the XCT and MRI images between the PDD group and the PD group were compared, the incidence of sulcal widening was found to be higher in the PDD group. The partial volume effect due to the cortical atrophy leads to an underestimation of the cortical glucose metabolism. However, the contribution of cortical atrophy in the PDD group was thought to be not so much compared to other groups because the sulcal widening in the PDD group was less than 3 mm.

In the present study, we examined the cerebral glucose metabolism of demented patients with Parkinson's disease and calculated the rCMRGlc by placing one hundred regions of interest. In the demented patients, the cerebral glucose metabolism was diffusely decreased in all regions, especially in the angular gyrus, compared with those in the non-demented patients and the normal volunteers. These results suggest that diffuse glucose hypometabolism in the cerebral cortex may correlate with dementia in patients with Parkinson's disease.

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