Hypometabolism based on a cutoff point on the mini-mental state examination in Parkinson's disease

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Abstract

Objective: The aim of the present study was to evaluate cortical hypometabolism of the F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) based on a diagnostic cutoff point of the mini-mental state examination (MMSE) in de novo PD.*Methods:* We recruited 24 PD patients and 15 healthy controls to analyze FDG-PET. We divided the patients into two groups by the diagnostic cutoff point of MMSE for diagnosing dementia, with scores of≥25 vs. < 25. FDG-PET was processed using statistical parametric mapping (SPM) 8 running on Matlab 11. *Results:* Patients with a MMSE < 25 presented lower score in time orientation, serial sevens, language and pentagon copying of MMSE compared to patients with a MMSE ≥25. Compared to healthy controls, patients with a MMSE≥ 25 and < 25 showed a fronto-temporo-parietal hypometabolism, which was more extended in patients with a MMSE < 25. Difference in cortical hypometabolism between patients with a MMSE ≥25 and < 25 was found in the right inferior parietal lobule.
Conclusions: In the comparison by cutoff point of MMSE (25/24), hypometabolism in the right inferior parietal lobule suggests that the posterior cortical deficit is the main region ofde novo PD with cognitive impairment. Hypometabolism of right inferior parietal lobule is related to the damage of cerebral networkin de novo PD.

INTRODUCTION

Cognitive impairments can occur even in newly diagnosed, early stages of Parkinson's disease (PD).[1] Frontal/executive dysfunction is known to be the main cognitive impairments of PD patients, which may be attributed to the disruption of the frontostriatal circuitry[1,2] and is consistent with the anatomic model of basal ganglia thalamocortical circuits.[2] However, there is still considerable controversy about the pattern of cognitive impairments in PD because some reports suggest posterior cortical deficits[3,4]based on studies describing explicit memory impairment and visuospatial/constructional dysfunction in PD.[5,6]

[18]F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been used to assess regional cerebral glucose metabolism (rCMRglc) for the differentiation of the cognitive status of PD patients.[7]Nondemented patients or those with mild cognitive impairment (MCI) due to PD usually show hypometabolism in the parieto-occipital cortices.[7-9]However, hypometabolism of dementia in PD (PDD) tends to present in multiple and wide cortical areas, including the lateral frontal, posterior cingulate and parieto-temporo-occipital cortices.[8,10,11]

Despite its relative insensitivity to mild forms of cognitive impairment[12], the mini-mental state examination (MMSE) is the most popular primary diagnostic tool for identifying cognitively impaired PD or PDD.[13,14] Some recent reports have suggested a cutoff point for cognitive impairment or dementia.[13,15]

The aim of this study is to analyze the patterns of hypometabolism between two groups divided by the cutoff point of MMSE for cognitive impairment.

METHODS

Patients and clinical assessments

The study subjects were 24 patients who were

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newly diagnosed with PD without medications. They fulfilled the diagnostic criteria of the UK Parkinson's disease brain bank.[16] In addition, 15 age-matched healthy controls were enrolled for analysis of FDG-PET. The motor severity of PD was determined by the motor scale of the United Parkinson's Disease Rating Scale (mUPDRS) and the Hoehn-Yahr (HY) stage.[17,18] Patients were excluded if they showed atypical features or secondary causes of parkinsonism, which was determined by evidence of focal brain lesions, diffuse white matter hyperintensities or multiple lacunes in the basal ganglia by MRI. Patients with a history of the dementia with Lewy body (DLB)[19] or dementia with PD (PDD)[14] according to established diagnostic criteria were excluded. We used the pill questionnaire[14] to exclude demented patients. According to cutoff of the pill questionnaire[14], we ruled out the patients if the patient was no longer able to explainhis daily PD medication, or if their caregivers reported poor performance of activity of daily of living. The patient's age during examination, age ofonset, sex, disease duration, education, mUPDRS scores, HY stage and were determined. Wealso determined the Korean version of MMSE (MMSE)[20], clinical dementia rating scale (CDR)[21], CDR-Sum of box (CDR-SOB), global deterioration scale (GDS)[22] and geriatric depression scale.[23]Patients who were unable to perform complete cognitive tests were excluded.We divided 24 de novo PD patients into two groups based on the cutoff point of MMSE scores for cognitive impairment (25/24). The cutoff point of MMSE for cognitive impairment was based on an established previous report.[13]The protocol was approved by the Institutional Review Board of Busan Paik Hospital. We obtained written informed consents from all subjects participating in this study.

Imaging procedures

Acquisition of FDG-PET scan

In all patients and control, FDG-PET/CT scan studies were performed after informed consent had been obtained. After overnight fasting and withdrawal of antiparkinsonian medications, an FDG-PET/CT scan was performed in a quiet and dimly lit room with the subjects' eyes open. The PET/CT scans were performed on GE Discovery STE scanners (GE Healthcare, Milwaukee, WI, USA) using standard techniques. We administered 370 MBq 18F-FDG through an antecubital vein. Approximately 45-55 min after the administration

of F-18 FDG, a low-dose CT was carried out to correct attenuation and for localization by a continuous spiral technique using an eight-slice CT (100 kVp, 85mA). The emission data were acquired in three-dimensional mode with an axial FOV of 25 cm for 15 min. Images were reconstructed by full 3-D iterative algorithm (5 iterations, 20 subsets). Forty-seven PET slices were acquired using a 256×256 matrix with a slice thickness of 3.27 mm.

Statistical parametric mapping

PET images were converted from DICOM into analyze format using the MIPAV software and then processed using SPM8 (Statistical parametric mapping; Wellcome Department of Cognitive Neurology,Institute of Neurology, London) on Matlab 11(Mathworks, Inc., Natick, MA). A 12-parameter linear affine transformation and a non-linear three-dimensional deformation were applied to each subject scan to realign and spatially normalize images to a reference stereotactic template (Montreal Neurological Institute, McGillUniversity, Montreal). The normalized data were then smoothed using a Gaussian kernel at FWHM 8mm to account for individual variability in structure-function relation and to enhance the signal-to-noise ratio. Global normalization was performed using ANCOVA (analysis of covariance) to include the global covariate (age) as a nuisance effect in the general linear model. The threshold masking was set to 0.2. The meaningful brain areas were considered with the significance of cluster level uncorrected $p < 0.01$ including more than 100 voxels. To analyze rCMRglc, a group comparison was modeled between PD patients and control subjects. We also compared the glucose between the PD group with low MMSE and that with high MMSE.

Statistical analysis

Statistical comparisons of the parametric clinical items between groups were performed with the t-test for continuous variables. The nonparametric variables were analyzed by Fisher's exact test. We did not considercovariate analyses because of small sample size. $P < 0.05$ was considered statistically significant.

RESULTS

Subject characteristics

There were no differences in age and education

between healthy controls and all PD patients. The ratio of man to woman is higher among the healthy controls as compared to PD patients. MMSE were significantly higher in healthy controls than in PD patients. Attention, memory, language and visuospatial functions were of lower scores in PD patients than healthy controls. The characteristics of de novoPD patients classified as patients with a MMSE$\geq$ 25 and < 25 based on the cutoff point are listed in Table 1. Age (68.0$\pm$ 4.56), age of onset (66.3$\pm$ 4.56), CDR-SOB (1.9 $\pm$ 1.29) and GDS (3.2 $\pm$ 0.63) of the patients with a MMSE < 25 were of higher scores than those (61.4 $\pm$ 8.0,59.2 $\pm$ 7.37, 0.63 $\pm$ 0.57, and 2.42$\pm$ 1.0, respectively) of the patients with a MMSE$\geq$ 25. Patients with a MMSE <25 showed higher prevalence of women compared to patients with a MMSE$\geq$25. Among sub-items of MMSE, time orientation, serial sevens, language function and pentagon copying showed significant low scores in patients with a MMSE < 25 compared to patients with a MMSE$\geq$ 25 (Table 1).There were also no significant difference in the sex, disease duration, education, HY stage, UPDRS motor score, CDR, frequency of depression and depression score.

Hypometabolism

In comparison with control, patients with a MMSE$\geq$ 25 showed significant hypometabolism in bilateral middle frontal gyri, right inferior parietal lobule and supplementary motor area, and left superior temporal and lingual gyri (Table 2; Figure 1a). The left superior temporal gyrus showed the widest voxels of hypometabolism (Table 2; Figure 1a).

Patients with a MMSE < 25 showed cortical hypometabolism in the bilateral middle frontal gyri, right cingulate gyrus, left inferior parietal lobule, middle temporal and fusiform gyri, and left posterior cingulate and caudate lobes in comparison with control (Table 2; Figure 1b). Hypometabolism in the right middle frontal gyrus is the largest voxels compared with other areas (Table 2; Figure 1b).

Patients with a MMSE$\geq$ 25 as compared to those< 25 showed hypometabolism in the right inferior parietal lobule (Table 2; Figure 1c).

DISCUSSION

In our study, de novo PD patients below the cutoff points for cognitive impairment (< 25) were older and had an older age of onset than patients above the cutoff ($\geq$25). This is similar to the results reported in other studies, which showed that dementia due to PD is associated with older age or older age of onset.[24]

It is known that men has higher prevalence of PD than women.[25]However, some reports suggested that women had poorer scores in cognitive assessments than men.[26,27]The longer survival of women may also partly contribute to higher proportion of women with MMSE<25.[28]

The CDR-SOB score has been considered to be a more detailed quantitative general index than the global score[29] and provides more information than the global CDR score in patients with mild dementia.[30] The GDS is also a generalizable and potentially widely applicable global measure for the assessment of cognitive decline secondary to primary degenerative dementia.[22] In our study, the CDR-SOB and GDS show significantly higher scores in patients below the diagnostic cutoff point. This result shows that the diagnostic cutoff point (25/24) reflects dementia severity by CDR-SOB and GDS in de novo PD.

There are several diverse results of brain hypometabolism in non-dementia, early stage PD patients (PD-non-dementia). Some FDG-PET studies of PD-non-dementia reported hypometabolism in the parieto-occipital cortices.[7,8]Other studies suggested frontal-type dysfunction in newly diagnosed, nonmedicated PD.[31] In one study, PD had extensive cortical hypometabolism, even during early disease stages.[32]Another study found that there were no hypometabolic brain regions in the PD-non-dementia patients compared to control subjects.[9] In our study, patients with a MMSE $\geq$ 25 showed the largest hypometabolism in the left superior temporal gyrus. In contrast, hypometabolism of the right middle frontal gyrus appears to have the largest voxels in patients with a MMSE < 25. The patients with a MMSE < 25 also show cortical hypometabolism in multiple and more extended areas than the patients with a MMSE $\geq$ 25. As previously reported[31,33], our patients with early stage PD showed hypometabolism in the frontal area and posterior cortical regions.

A significant difference of hypometabolism between the patients with a MMSE $\geq$ 25 and < 25 was only detected in the right inferior parietal lobule. Neuroimaging studies in PD-MCI showed dysfunction in parietal and occipital cortices.[9,34] In addition, hypometabolism shows more widespread cortical areas in PDD.[34]These findings support that posterior cortical regions, including right inferior parietal lobe in our study, plays an important role in the development or progression of dementia in PD. In addition, our study also supports that the

Table 1: Demographic features and clinical characteristics of de novo Parkinson's disease according to the cutoff point of the mini-mental state examination (MMSE)

	Healthy control (n = 15)	Participants with PD (n = 24)	p-value	MMSE ≥ 25 (n = 13)	MMSE < 25 (n = 11)	p-value
Age (y)	65.7 ± 3.7	64.5 ± 7.3	0.56	61.5 ± 7.9	68.0 ± 4.6	**0.03**
Sex, men	10	9	0.1	7	2	0.11
Age at onset (y)		62.7 ± 7.1		59.3 ± 7.3	66.6 ± 4.3	**0.008**
Disease duration (m)		4.2 ± 6.2		3.2 ± 2.1	5.4 ± 9.0	0.46
Education (y)	8.6 ± 3.6	7.8 ± 4.8	0.55	8.1 ± 4.5	8.2 ± 4.8	0.95
HY stage		2.2 ± 0.8		2.1 ± 0.8	2.2 ± 0.7	0.84
UPDRS motor score		22.1 ± 11.1		23.5 ± 12.1	20.4 ± 10.0	0.5
MMSE total score	28.8 ± 1.1	23.9 ± 5.5	**0.001**	28.0 ± 1.4	19.0 ± 4.24	**0.0001**
Time orientation	4.3 ± 0.9	4.0 ± 1.2	0.335	4.8 ± 0.4	3.0 ± 1.2	**0.0001**
Place orientation	4.9 ± 0.4	4.5 ± 0.9	0.183	4.9 ± 0.3	4.1 ± 1.2	0.06
Memory-registration	3.0 ± 0.0	2.9 ± 0.3	0.162	3.0 ± 0.0	2.8 ± 0.4	0.17
Serial sevens	4.8 ± 0.4	2.6 ± 2.1	**0.0001**	4.3 ± 1.1	0.8 ± 1.1	**0.0001**
Memory-recall	2.8 ± 0.4	2.0 ± 1.0	**0.004**	2.3 ± 0.7	1.7 ± 1.2	0.19
Language	7.6 ± 0.5	6.8 ± 1.5	**0.024**	7.6 ± 0.7	0.7 ± 1.6	**0.005**
Pentagon copy	1.0 ± 0.0	0.7 ± 0.5	**0.011**	0.9 ± 0.3	0.5 ± 0.5	**0.04**
CDR	NI	0.5 ± 0.3		0.4± 0.2	0.6 ± 0.2	**0.01**
CDR-SOB	NI	1.5 ± 1.8		0.7 ± 0.6	2.5 ± 2.2	**0.02**
GDS	NI	2.8 ± 1.1		2.2 ± 1.0	3.4 ± 0.8	**0.007**
Depression (%)	NI	17 (70.8)		9 (37.5)	8 (33.3)	1.0
Geriatric depression score	NI	20.0 ± 8.5		21.0 ± 7.9	18.7 ± 9.3	0.52

PD, Parkinson's disease; MMSE, Mini-Mental State Examination; HY, Hoehn-Yahr; UPDRS, United Parkinson's Disease Rating Scale; CDR, Clinical Dementia Rating; CDR-SOB, Clinical Dementia Rating-Sum of box; GDS, global deterioration scale; y, year; m, month; NI, no information

early involvement of posterior cortical regions, a pattern shared by advanced stages of PD-MCI and PDD, could represent anearly marker of dementia.[35]Of cognitive subsets of MMSE, time orientation, attention (serial sevens), language and visuospatial function (pentagon copying) are significantly low in patients with a MMSE < 25. These findings suggest that right parietal lobule leads to deficit multiple cognitive impairment in de novo PD and is broadly connected with various cortical regions as well as the dorsal stream, which is dedicated to the processing of spatial
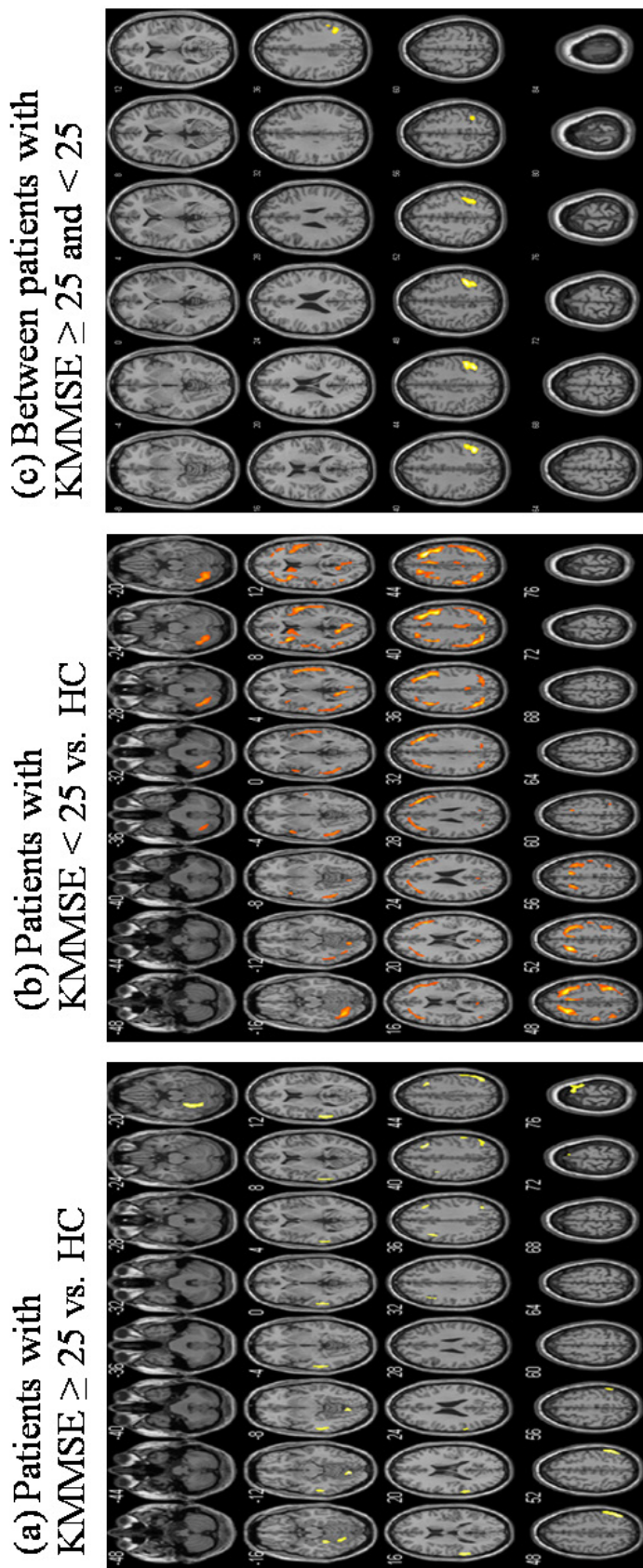
(a) Patients with KMMSE ≥ 25 vs. HC

(b) Patients with KMMSE < 25 vs. HC

(c) Between patients with KMMSE ≥ 25 and < 25

Figure 1. SPM analysis, p < 0.01, corrected. (a) Between patients with a MMSE ≥ 25 and control, (b) Between patients with a MMSE < 25 and control, (c) Between patients with a MMSE ≥ 25 and < 25.

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Table 2: The regional differences in hypometabolism between groups

	Regions	MNI coordinate			Cluster size (voxels)	t-value
		x	y	z		
MMSE ≥25 vs. controls	Lt. superior temporal gyrus	-60	-38	16	**510**	3.1543
	Rt. Inferior parietal lobule	52	-62	48	457	3.2549
	Lt. lingual gyrus	-4	-76	-10	325	3.6184
	Right supplementary motor area	32	-24	80	289	3.4625
	Rt. middle frontal gyrus	34	24	42	106	3.486
	Lt. middle frontal gyrus	-40	16	34	100	3.3108
MMSE < 25 vs. controls	Rt. middle frontal gyrus	34	20	44	**4621**	7.4859
	Lt. middle frontal gyrus	-24	14	50	**1762**	7.1375
	Lt. fusiform gyrus	-32	-70	-16	1050	4.7062
	Lt. inferior parietal lobule	-42	-58	38	986	5.923
	Lt. middle temporal gyrus	-44	-64	8	773	4.1977
	Lt. posterior cingulate	-10	-60	6	429	4.7205
	Rt. cingulate gyrus	6	-30	42	192	3.2916
	Lt. caudate	-14	18	10	163	3.2137
MMSE ≥25 vs.< 25	Rt. inferior parietal lobule	42	-52	42	**635**	4.6273

PD, Parkinson's disease; MMSE, Mini-Mental State Examination; Rt., right; Lt., left; MNI coordinate, Montreal Neurological Institute and Hospital coordinate system

information (the 'where' pathway).[36,37]

Our study confirmed that posterior cortical regions were significantly associated with cognitive function in PD patients. Nevertheless, our studyhad some limitations. First, there were gender difference between healthy controls and PD patients. Second, there were significant difference in age between PD patients with MMSE≥ 25 and <25. These findings could have a limited influence on the hypometabolism in the more widespread and multiple brain regions of patients with MMSE <25 compared to patients with MMSE≥25. These limitations may be associatedwith small sample size.

In summary, we found that the cutoff point of MMSE for cognitive impairment is associated with a difference in hypometabolism according to severity of cognitive deficits in the early and de novo PD patients.

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DISCLOSURE

Conflict of interest: None

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