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ORIGINAL ARTICLE

Impact of Additional Occipital Involvement in Parkinson's Disease With Posterior Cortical Hypoperfusion

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ABSTRACT

Objective This study aims to investigate the clinical relevance of occipital hypoperfusion in patients with Parkinson's disease (PD) with respect to clinical phenotype and the risk of dementia conversion.

Methods We enrolled 349 patients with newly diagnosed PD and 48 healthy controls who underwent dual-phase ^{18}F-N-(3-fluoropropyl)-2β-carboxymethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET). Patients with PD were classified into three groups based on posterior cortical perfusion patterns on early-phase ^{18}F-FP-CIT PET images: PD with preserved posterior cortical perfusion (*n*=186), PD with parieto-temporal hypoperfusion (*n*=84), and PD with parieto-temporo-occipital hypoperfusion (*n*=79). Baseline clinical features and dementia conversion risk were compared across PD groups.

Results Patients with preserved posterior cortical perfusion were younger than those in the other PD groups. Compared with the other groups, the parieto-temporo-occipital hypoperfusion group tended to have lower Cross-Cultural Smell Identification Test scores, a higher prevalence of rapid eye movement sleep behavior disorder, higher Unified PD Rating Scale motor scores, and more severe reductions in striatal dopamine transporter availability. The risk of dementia conversion was lower in patients with preserved posterior cortical perfusion than in those with posterior cortical hypoperfusion. However, the risk of dementia conversion did not differ between the parieto-temporal and parieto-temporo-occipital hypoperfusion groups.

Conclusion Additional occipital hypoperfusion was not associated with an imminent risk of dementia conversion in patients with PD with posterior cortical hypoperfusion. Nonetheless, occipital involvement may serve as an indicator of the diffuse malignant subtype of PD.

Keywords Dementia; Dual-phase ^{18}F-FP-CIT PET; Occipital hypoperfusion; Parkinson's disease; Posterior cortical hypoperfusion.

INTRODUCTION

Occipital hypometabolism or hypoperfusion is a supportive imaging biomarker suggestive of dementia with Lewy bodies (DLB),[1,2] and it is correlated with neuropathological changes in this region, such as spongiform degeneration and gliosis, in patients with DLB.[3] Evidence indicates that measurements of glucose metabolism or cerebral perfusion in the occipital cor-

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tex can serve as valuable diagnostic tools for distinguishing DLB from Alzheimer's disease.[2,3] Occipital hypometabolism or hypoperfusion is also frequently observed in patients with Parkinson's disease (PD),[4-7] which shares the pathological hallmark of Lewy bodies with DLB. However, the pathological basis and clinical significance of occipital dysfunction in patients with PD remain incompletely understood. Considering the "1-year rule" used to differentiate PD from DLB,[2] it is reasonable to hypothesize that occipital hypoperfusion may act as a marker of imminent dementia conversion or a transitional state preceding dementia in patients with PD. Furthermore, our previous study demonstrated that occipital hypoperfusion is associated with lower motor reserve in PD patients,[4] suggesting that it may reflect a broader pathological burden extending beyond the nigrostriatal pathway.

Traditionally, posterior cortical hypoperfusion is considered a good predictor of early dementia conversion in patients with PD.[6-11] In our previous study using cluster analysis to classify patients with PD according to regional cerebral perfusion patterns, we identified a subgroup that exhibited additional occipital hypoperfusion superimposed on parieto-temporal hypoperfusion.[5] Although this subgroup had a higher risk of dementia conversion than a subgroup with relatively preserved cerebral perfusion, our previous study did not clearly elucidate the clinical relevance of occipital involvement. Therefore, in the present study, we classified patients with PD according to regional cerebral perfusion patterns based on a hypothesis-driven rather than a data-driven approach.

We hypothesized that occipital hypoperfusion in PD patients represents an unfavorable condition with respect to both clinical phenotype and the risk of dementia conversion. To test this hypothesis, we used early-phase ^{18}F-N-(3-fluoropropyl)-2β-carboxymethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET) imaging to assess alterations in regional cerebral perfusion in 349 patients with early-stage PD.[12,13] Based on the observation that posterior cortical hypoperfusion in PD patients occurs in two distinct patterns, one with additional occipital involvement and one without prominent occipital involvement (Figure 1), patients were classified into three groups: PD with preserved posterior cortical perfusion, PD with parieto-temporal hypoperfusion, and PD with parieto-temporo-occipital hypoperfusion. We then examined whether the presence of occipital hypoperfusion, in addition to parieto-temporal hypoperfusion, has clinical relevance and provides prognostic value for future cognitive decline in patients with newly diagnosed PD.

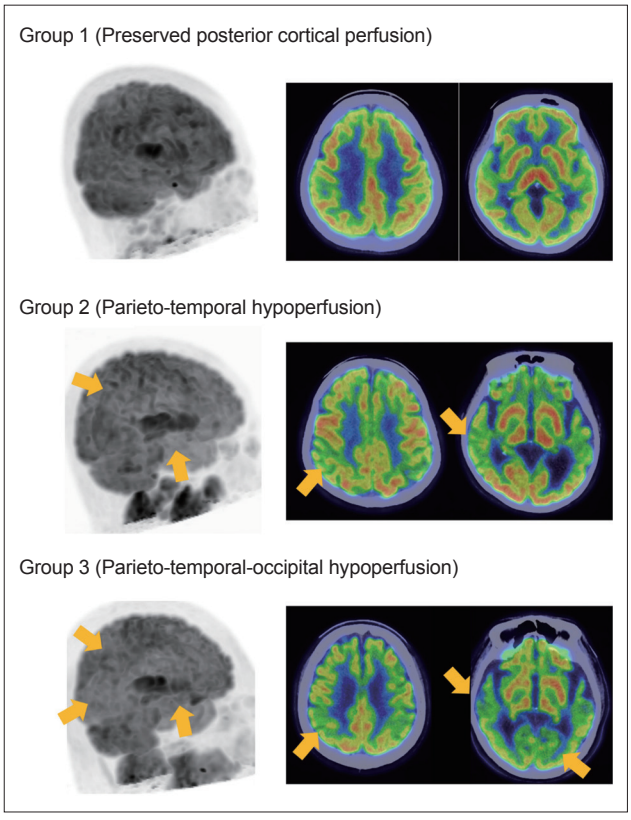

Figure 1. Schematic representations of the early-phase ^{18}F-FP-CIT PET images for each PD group. ^{18}F-FP-CIT PET, ^{18}F-N-(3-fluoropropyl)-2β-carboxymethoxy-3β-(4-iodophenyl) nortropane positron emission tomography; PD, Parkinson's disease.

MATERIALS & METHODS

Participants

We retrospectively reviewed the medical records of 384 consecutive, drug-naïve patients with nondemented PD who visited the Movement Disorders outpatient clinic between January 2015 and November 2018. The diagnosis of PD was made according to the Movement Disorder Society clinical diagnostic criteria.[14] All patients underwent dual-phase ^{18}F-FP-CIT PET at the time of diagnosis and demonstrated appropriate reductions in striatal dopamine transporter (DAT) availability on late-phase ^{18}F-FP-CIT PET scans. During follow-up (median duration, 6.10 years), none of the patients developed atypical features, such as poor response to dopaminergic medications, ataxia, prominent autonomic dysfunction, vertical gaze limitation, early falls, or cortical sensory deficits. At the time of ^{18}F-FP-CIT PET acquisition, motor severity was assessed using the Unified PD Rating Scale Part III (UPDRS-III), and motor subtypes were classified as tremor-dominant, postural instability/gait difficulty, or indeterminate.[15] Olfactory function and depression were evaluated using the Cross-Cultural Smell Identification Test (CCSIT) and

the Beck Depression Inventory (BDI), respectively. The presence of rapid eye movement sleep behavior disorder (RBD) was determined using an RBD screening questionnaire, with a cut-off score of ≥6.[16] The severity of white matter hyperintensity (WMH) was rated on fluid-attenuated inversion recovery magnetic resonance imaging (MRI) using the Scheltens scale.[17] A standardized neuropsychological battery test (i.e., the Seoul Neuropsychological Screening Battery[18]; Supplementary Material) was administered to calculate cognitive composite scores, derived by dividing the sum of z-scores by the number of tests within each cognitive domain. General cognition was assessed using the Korean version of the Mini-Mental State Examination (K-MMSE).[19] Additionally, 48 healthy individuals (mean age, 68.60±7.89 years; female, 50.0%) who voluntarily participated in this study and underwent brain MRI and dual-phase ^{18}F-FP-CIT PET served as controls. The study was approved by the Institutional Review Board of Yonsei University Severance Hospital (No. 4-2022-1421). Requirements for informed consent were waived owing to the retrospective study design.

Quantitative analyses of ^{18}F-FP-CIT PET images

Acquisition of dual-phase ^{18}F-FP-CIT PET images was performed according to previously described methodology (Supplementary Material).[20]

Early-phase ^{18}F-FP-CIT PET images

Image processing was conducted using MATLAB (MathWorks, Inc.) software for Statistical Parametric Mapping 12 (https://www.fil.ion.ucl.ac.uk/spm/) and FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu). Early-phase ^{18}F-FP-CIT PET images were coregistered to T1-weighted MRI (Supplementary Material) and spatially normalized to the Montreal Neurological Institute template (McGill University). Standardized uptake value ratio (SUVR) values were calculated using the global mean normalization method.[21,22] In addition, T1-weighted images were parcellated according to the Desikan–Killiany atlas in FreeSurfer, and SUVRs were extracted from the corresponding regions of interest (ROIs). The parieto-temporal region comprises the superior/inferior parietal lobules, supramarginal gyrus, postcentral gyrus, precuneus, superior/middle/inferior temporal gyri, transverse temporal gyrus, and fusiform gyrus. The occipital region comprises the lateral occipital, cuneus, pericalcarine, and lingual cortices.

Late-phase ^{18}F-FP-CIT PET images

Quantitative analyses of late-phase ^{18}F-FP-CIT PET images were performed as described in our previous studies (Supplementary Material).[20,23,24] The striatum was segmented into the anterior and posterior caudate, anterior and posterior putamen, ventral putamen, and ventral striatum. DAT availability in each striatal subregion was estimated using the specific-to-nonspecific binding ratio, defined as (mean uptake in the striatal volume-of-interest [VOI]−mean uptake in the occipital VOI)/mean uptake in the occipital VOI.

Classification of PD patients based on the posterior cortical SUVR

After the early-phase ^{18}F-FP-CIT PET images were quantified, parieto-temporal and occipital SUVRs were calculated for each patient. Patients with PD were classified into three groups according to the pattern of posterior cortical perfusion: 1) PD with relatively preserved posterior cortical perfusion (Group 1, n=186); 2) PD with parieto-temporal hypoperfusion (i.e., 1 SD below the mean parieto-temporal SUVR of healthy controls with relatively preserved occipital perfusion; Group 2, n=84); and 3) PD with parieto-temporo-occipital hypoperfusion (1 SD below the mean parieto-temporal SUVR and occipital SUVR of healthy controls; Group 3, n=79). The remaining 39 patients exhibited occipital hypoperfusion with relatively preserved parieto-temporal perfusion; however, these patients were excluded because the study focused on the clinical relevance of additional occipital involvement in PD with posterior cortical hypoperfusion. In fact, occipital hypoperfusion or hypometabolism typically occurs together with parieto-temporal involvement in patients with PD or DLB,[1,5,25,26] suggesting that an isolated occipital pattern may not represent a distinct biological subtype within the clinical spectrum of these disorders. In addition, although regional cerebral perfusion in the frontal region was more severely decreased in the PD groups with posterior cortical hypoperfusion than in the PD group with relatively preserved posterior cortical perfusion, the frontal region was not included in the analysis. The final study population therefore consisted of 349 participants, and schematic representations of the early-phase ^{18}F-FP-CIT PET images for each PD group are shown in Figure 1.

Assessment of dementia conversion during follow-up

After PD diagnosis, patients visited the outpatient clinic every 3 months, where two movement disorder specialists (PHL and YHS) evaluated dementia conversion during follow-up, as previously described (Supplementary Material).[27] The diagnosis of Parkinson's disease with dementia (PDD) was given by consensus between two neurologists and one neuropsychologist based on the clinical diagnostic criteria proposed by the Movement Disorder Society Task Force.[28]

Statistical analysis

Baseline demographic characteristics and cognitive perfor-

mance were compared among the PD groups using one-way analysis of variance (ANOVA) for continuous variables and Pearson's χ^2 tests for categorical variables. Striatal DAT availability was compared using analysis of covariance (ANCOVA) with age and sex as covariates. Multiple comparisons after ANOVA or ANCOVA were corrected using the Bonferroni method. The time from ^{18}F-FP-CIT PET acquisition to dementia conversion was assessed using Kaplan–Meier estimates, and group differences were evaluated with the log-rank test. Cox regression models were then applied to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of PDD conversion according to posterior cortical perfusion patterns. Three models were constructed: Model 1 assessed the effect of parieto-temporal SUVR on PDD risk; Model 2 assessed the effect of parieto-temporo-occipital SUVR on PDD risk; and Model 3 compared dementia-free survival times across PD groups. All the models were adjusted for age at PD onset, sex, UPDRS-III score, DAT availability in the associative striatum (caudate and anterior putamen), and educational attainment. Statistical analyses were performed using SPSS software (version 26.0; IBM Corp.) and R software (version 4.0; The R Foundation, http://www.r-project.org/). Two-tailed p values <0.05 were considered to indicate statistical significance.

RESULTS

Baseline clinical characteristics of patients with PD

Table 1 summarizes the baseline clinical characteristics of each PD group. Patients with relatively preserved posterior cortical perfusion (Group 1, n=186) had a younger age at onset (64.50±9.89 years), less severe WMH burden (10.35±6.99, assessed using the Scheltens scale), and better cognitive performance (K-MMSE score, 27.13±2.96) as well as a lower prevalence of mild cognitive impairment (37.6%) than those in the other PD groups. Compared with the other PD groups, the parieto-temporal hypoperfusion group (Group 2, n=84) had a greater proportion of the PIGD subtype (53.6%). Compared with the other groups, the parieto-temporo-occipital hypoperfusion group (Group 3, n=79) had lower CCSIT scores (5.46±2.70) and a higher prevalence of RBD (49.4%). In addition, Group 3 patients had higher UPDRS-III scores (25.72±10.22) and lower composite scores (-0.62±0.91) for verbal memory and frontal/executive function (-0.79±0.87) than Group 1 patients (UPDRS-III score, 21.23±9.45; p=0.001; verbal memory score, -0.21±0.91; p=0.024; frontal/executive function score, -0.48±0.77; p=0.046). No significant group differences were observed for sex, disease duration, years of education, or BDI scores.

Table 2 shows the striatal DAT availability across groups. Compared with Group 1 patients, Group 3 patients exhibited significantly lower DAT availability in the anterior putamen (estimated mean [standard error], 2.43 [0.08] vs. 2.67 [0.05], p=0.047) and a nonsignificant trend toward lower values in the anterior caudate (2.46 [0.08] vs. 2.68 [0.50], p=0.072) and ventral striatum (2.12 [0.06] vs. 2.28 [0.04], p=0.082). Compared with Group 2 patients, Group 3 patients tended to have lower DAT availability in the posterior caudate (1.58 [0.06] vs. 1.75 [0.05], p=0.061), anterior putamen (2.43 [0.08] vs. 2.68 [0.08], p=0.054), and ventral putamen (1.76 [0.06] vs. 1.93 [0.05], p=0.064), although these differences were not statistically significant. No significant group differences were found in the posterior putamen.

Effects of posterior cortical perfusion patterns on dementia conversion

During the follow-up period (median duration, 6.10 years), dementia developed in 28 of 186 patients (15.1%) with relatively preserved posterior cortical perfusion (Group 1), 32 of 84 patients (38.1%) with parieto-temporal hypoperfusion (Group 2), and 32 of 79 patients (40.5%) with parieto-temporo-occipital hypoperfusion (Group 3). The log-rank test revealed that patients in Group 1 had a significantly lower risk of dementia conversion than those in Groups 2 and 3 (with posterior cortical hypoperfusion; p<0.001). However, no significant difference was observed between Groups 2 and 3 (p=0.817) (Figure 2).

Cox regression models further demonstrated that lower SUVR values in both the parieto-temporal region (Model 1 in Table 3) and the parieto-temporo-occipital region (Model 2 in Table 3) were associated with a greater risk of dementia conversion (p<0.001 and p=0.002, respectively). In Model 3 (Table 3), which included the PD groups, patients in Group 1 had a lower risk of PDD conversion than those in Group 2 (HR, 2.079; 95% CI, 1.184–3.649; p=0.011) and trended toward a lower risk than those in Group 3 (HR, 1.611; 95% CI, 0.914–2.839; p=0.099). Moreover, the risk of dementia conversion did not differ significantly between Groups 2 and 3 (p=0.336).

DISCUSSION

This study examined the clinical relevance of occipital hypoperfusion in patients with PD with respect to clinical phenotype and the risk of dementia conversion. The main findings were as follows: 1) the PD group with parieto-temporo-occipital hypoperfusion exhibited a more malignant clinical phenotype, characterized by higher UPDRS-III scores, lower CCSIT scores, a higher prevalence of RBD, and more severely reduced DAT

Table 1. Baseline clinical characteristics in patients with PD

	Group 1 (*n*=186)	Group 2 (*n*=84)	Group 3 (*n*=79)	*p*-value‡	1 vs. 2§	1 vs. 3§	2 vs. 3§
Demographic characteristics							
Age (yr)	66.07±9.59	75.61±8.04	76.41±7.27	<0.001	<0.001	<0.001	>0.999
Onset age (yr)	64.50±9.89	74.01±8.03	74.88±7.26	<0.001	<0.001	<0.001	>0.999
Female	105 (56.5)	41 (48.8)	33 (41.8)	0.080			
PD duration (months)	19.16±18.21	18.85±17.67	18.02±14.11	0.885	>0.999	>0.999	>0.999
UPDRS-III	21.23±9.45	22.76±8.55	25.72±10.22	0.002	0.650	0.001	0.138
Education (yr)	10.52±4.53	9.58±5.67	10.28±5.11	0.431	0.482	>0.999	>0.999
Motor subtype				0.020			
Tremor dominant	82 (44.1)	32 (38.1)	27 (34.2)				
PIGD	68 (36.6)	45 (53.6)	33 (41.8)				
Indeterminate	36 (19.4)	7 (8.3)	19 (24.1)				
CCSIT	7.30±2.32	6.53±2.50	5.46±2.70	<0.001	0.079	<0.001	0.030
BDI	12.33±9.21	12.03±9.33	12.76±8.07	0.880	>0.999	>0.999	>0.999
RBD	48 (25.8)	20 (23.8)	39 (49.4)	<0.001			
Vascular risk factors							
Hypertension	77 (41.4)	46 (54.8)	34 (43.0)	0.115			
Diabetes mellitus	33 (17.7)	29 (34.5)	25 (31.6)	0.004			
Dyslipidemia	38 (20.4)	29 (34.5)	21 (26.6)	0.045			
Body mass index	24.01±3.22	23.39±3.48	23.71±3.11	0.173	0.391	0.389	>0.999
Total WMH burden*	10.35±6.99	14.49±7.66	14.57±8.05	<0.001	<0.001	<0.001	>0.999
Level of cognitive performance†							
MCI proportion	70 (37.6)	39 (46.4)	42 (53.2)	0.052			
K-MMSE	27.13±2.96	25.14±4.12	25.30±4.21	0.097	<0.001	<0.001	>0.999
Attention/working memory	-0.07±0.77	-0.35±0.82	-0.10±0.97	0.103	0.116	>0.999	0.304
Language	-0.35±1.24	-0.63±1.31	-0.40±1.24	0.383	0.519	>0.999	0.949
Visuospatial	-0.35±1.39	-0.66±1.59	-0.94±2.23	0.081	0.772	0.084	>0.999
Verbal memory	-0.21±0.91	-0.43±1.10	-0.62±0.91	0.020	0.475	0.024	0.899
Visual memory	-0.21±0.87	-0.52±0.84	-0.50±0.85	0.037	0.097	0.111	>0.999
Frontal/executive	-0.48±0.77	-0.72±0.81	-0.79±0.87	0.034	0.203	0.046	>0.999

The values are expressed as mean±standard deviation or number (percentage).
*the WMH severity was rated on FLAIR images using the Scheltens scale[17]; †233 patients (116 in group 1, 56 in group 2, and 61 in group 3) underwent a detailed neuropsychological test at initial assessment; ‡*p*-value from ANOVA; §Bonferroni correction *p*-values of the post-hoc comparison test.
PD, Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; PIGD, postural instability/gait difficulty; CCSIT, Cross-Cultural Smell Identification Test; BDI, Beck Depression Inventory; RBD, rapid eye movement sleep behavior disorder; WMH, white matter hyperintensity; MCI, mild cognitive impairment; K-MMSE, Korean version of the Mini-Mental State Examination.

Table 2. Striatal DAT availability in patients with PD

	Group 1 (*n*=186)	Group 2 (*n*=84)	Group 3 (*n*=79)	*p*-value*	1 vs. 2†	1 vs. 3†	2 vs. 3†
Anterior caudate	2.68 (0.50)	2.68 (0.07)	2.46 (0.08)	0.046	>0.999	0.072	0.103
Posterior caudate	1.72 (0.04)	1.75 (0.05)	1.58 (0.06)	0.043	>0.999	0.109	0.061
Anterior putamen	2.67 (0.05)	2.68 (0.08)	2.43 (0.08)	0.026	>0.999	0.047	0.054
Posterior putamen	1.84 (0.05)	1.87 (0.07)	1.66 (0.07)	0.064	>0.999	0.158	0.089
Ventral putamen	1.90 (0.04)	1.93 (0.05)	1.76 (0.06)	0.044	>0.999	0.108	0.064
Ventral striatum	2.28 (0.04)	2.26 (0.06)	2.12 (0.06)	0.071	>0.999	0.082	0.226

The values are expressed as estimated mean (standard error).
**p*-value from ANCOVA, while adjusting for age and sex; †Bonferroni correction *p*-values of the post-hoc comparison test.
DAT, dopamine transporter; PD, Parkinson's disease; ANCOVA, analysis of covariance.

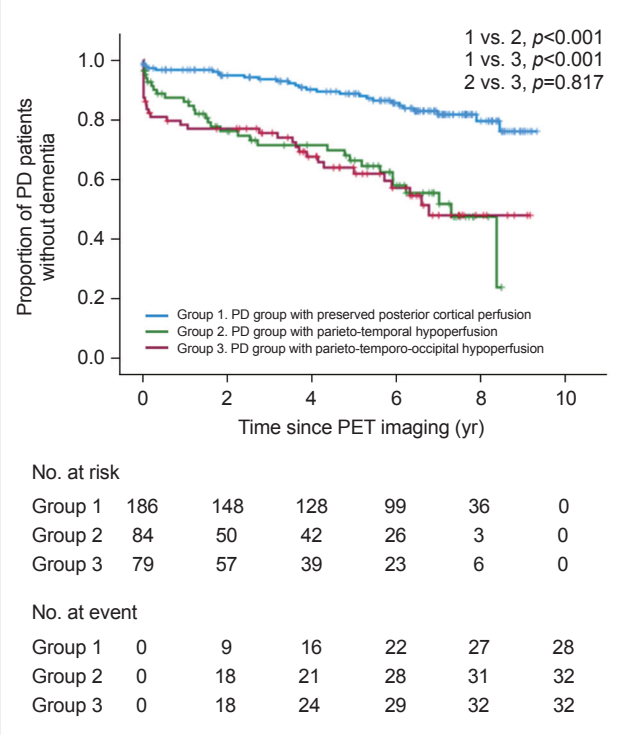

Figure 2. Kaplan–Meier curves for dementia conversion after ^{18}F-FP-CIT PET acquisition in patients with PD. Compared with the PD groups with posterior cortical hypoperfusion, the PD group with relatively preserved posterior cortical perfusion (n=186) had a lower risk of dementia conversion. Moreover, the risk of dementia conversion did not differ between the parieto-temporal hypoperfusion group (n=84) and the parieto-temporo-occipital hypoperfusion group (n=79; $p_{log\text{-}rank}$= 0.817). The crosses in the graphs indicate censored data. The p-values shown on the plot were derived from the log-rank test (unadjusted). The estimated HRs from Cox regression models while adjusting for potential confounding factors were as follows: Group 2 vs. 1, HR= 2.079, 95% CI=1.184–3.649, p=0.011; Group 3 vs. 1, HR=1.611, 95% CI=0.914–2.839, p=0.099; Group 2 vs. 3, HR=1.290, 95% CI=0.768–2.169, p=0.336. PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval; PET, positron emission tomography.

Table 3. Cox regression analysis for conversion to dementia

	Hazard ratio (95% CI)	*p*-value
Model 1		
SUVR on parieto-temporal region	0.000 (0.000–0.008)	<0.001
Age at PD onset	1.055 (1.032–1.079)	<0.001
Sex (Male vs. Female)	1.225 (0.763–1.966)	0.402
UPDRS-III	1.008 (0.986–1.032)	0.478
DAT availability in the associative striatum	0.396 (0.266–0.589)	<0.001
Years of education	0.958 (0.914–1.004)	0.071
Model 2		
SUVR on parieto-temporo-occipital region	0.000 (0.000–0.046)	0.002
Age at PD onset	1.057 (1.034–1.081)	<0.001
Sex (Male vs. Female)	1.345 (0.838–2.159)	0.219
UPDRS-III	1.012 (0.990–1.035)	0.294
DAT availability in the associative striatum	0.384 (0.257–0.575)	<0.001
Years of education	0.956 (0.912–1.002)	0.060
Model 3		
PD groups		0.038
Group 2 vs. Group 1	2.079 (1.184–3.649)	0.011
Group 3 vs. Group 1	1.611 (0.914–2.839)	0.099
Group 2 vs. Group 3	1.290 (0.768–2.169)	0.336
Age at PD onset	1.056 (1.033–1.079)	<0.001
Sex (Male vs. Female)	1.261 (0.782–2.034)	0.342
UPDRS-III	1.010 (0.988–1.033)	0.366
DAT availability in the associative striatum	0.376 (0.249–0.569)	<0.001
Years of education	0.962 (0.918–1.008)	0.100

SUVR, standardized uptake value ratio; PD, Parkinson's disease; UPDRS-III, Unified PD Rating Scale Part III; DAT, dopamine transporter; CI, confidence interval.

availability in the associative and limbic striatum than the other PD groups; and 2) the risk of dementia conversion was lower in the PD group with relatively preserved posterior cortical perfusion than in the PD groups with posterior cortical hypoperfusion, while no significant difference was observed between the parieto-temporal and parieto-temporo-occipital hypoperfusion groups. Taken together, these findings suggest that additional hypoperfusion in the occipital region is not associated with an imminent risk of dementia conversion in patients with PD with posterior cortical hypoperfusion, although occipital involvement may serve as an indicator of the diffuse malignant subtype of PD.

Our findings highlight the prognostic significance of posterior cortical hypoperfusion in PD. Patients with parieto-temporal hypoperfusion, regardless of occipital involvement, were at increased risk of dementia conversion. This observation is consistent with the results of previous neuroimaging studies showing that posterior cortical hypometabolism or hypoperfusion is an early feature preceding dementia in patients with PD.[5,7,9,29] Alterations in posterior cortical activity may reflect cholinergic denervation secondary to degeneration of the nucleus basalis of Meynert,[30] and may also indicate a greater burden of neurodegenerative changes or PD-related pathologies.[3,29] In particular, reduced occipital activity is a well-established metabolic marker of DLB,[31] raising the expectation that occipital hypoperfusion in patients with PD would indicate impending dementia conversion. However, our results demonstrated that additional occipital hypoperfusion beyond the parieto-temporal regions did not further increase the risk of PDD conversion. In DLB, more extensive occipital hypometabolism has been linked to visual hallucinations,[32] likely driven by cholinergic deficits and Lewy body pathology in the visual cortex.[31] In contrast, few studies have examined the intrinsic pathological ba-

sis and prognostic relevance of occipital hypometabolism or hypoperfusion in PD. Our findings therefore suggest a potential divergence between PD and DLB, despite their clinical and pathological overlap within the Lewy body disease spectrum.[2,14,33] Furthermore, although the posterior cortical region is strongly associated with PDD,[6,7,34] the occipital region itself may not represent a pivotal neural substrate for dementia development in PD, consistent with our previous findings on the clinical implications of cluster analysis–derived patterns of regional cerebral hypoperfusion.[5]

Compared with the PD group with relatively preserved posterior cortical perfusion, the PD group with parieto-temporo-occipital hypoperfusion exhibited baseline clinical features resembling a diffuse malignant subtype,[35] including higher UPDRS-III scores, lower CCSIT scores, a higher prevalence of RBD, and lower composite scores in verbal memory and frontal/executive function domains. This finding is consistent with the notion that posterior cortical involvement, particularly in the occipital region, reflects a greater pathological burden in patients with PD.[4,20,36] Although direct evidence linking the occipital region to parkinsonian motor symptoms is lacking, our earlier studies showed that reduced occipital activity was associated with lower motor reserve (i.e., higher UPDRS-III scores despite similar levels of dopamine depletion in the posterior putamen) and poorer motor outcomes in patients with PD.[4,37] Moreover, evidence suggests that several nonmotor symptoms including hyposmia,[38] RBD,[36] as well as autonomic dysfunction,[20] are associated with occipital hypoperfusion or hypometabolism in patients with PD. Poorer cognitive performance in the parieto-temporo-occipital hypoperfusion group may be explained by posterior cortical dysfunction in line with the dual syndrome hypothesis.[39,40] In addition, more severe dopamine deficiency in the associative and ventral striatum, reflecting more widespread underlying pathology, may contribute to cognitive impairment. Indeed, frontal/executive dysfunction in patients with PD has been primarily linked to degeneration of the mesocortical dopaminergic system,[41,42] while memory dysfunction may result from dopaminergic denervation of the ventral striatum.[43]

Our study has several distinctive features and methodological advantages compared with previous literature reporting the association between occipital hypo-metabolism/-perfusion and cognitive impairment in PD. First, we used the early-phase of ^{18}F-FP-CIT PET as a surrogate for cerebral perfusion, enabling simultaneous assessment of dopaminergic and perfusion changes within a single imaging session. Second, we included drug-naïve, newly diagnosed PD patients, thereby minimizing the potential confounding effects of dopaminergic treatment or advanced disease. Third, our study utilized a PD cohort with longitudinal follow-up data rather than cross-sectional data, allowing us to explore the association between regional cerebral perfusion and ongoing cognitive decline. These aspects differentiate our study from prior investigations and provide more precise insights into the clinical implications of occipital hypoperfusion in early-stage PD patients.

This study has several limitations. First, although early-phase ^{18}F-FP-CIT PET images provide a convenient surrogate for cerebral perfusion, further validation is needed before they can be considered a reliable alternative to conventional perfusion imaging. Second, the follow-up duration was relatively short; dementia conversion may have occurred in some patients beyond the study period, and the prognostic impact of occipital hypoperfusion may have become apparent only over a longer timescale.[44] Additionally, although the PD group with parieto-temporo-occipital hypoperfusion tended to have an increased risk of dementia conversion compared with the PD group with relatively preserved posterior cortical perfusion, this difference did not reach statistical significance, which appears to contradict the results of the log-rank test. Although this finding may be attributable to potential confounding factors such as age, further studies with larger sample sizes and longer follow-up periods are needed to verify these findings. Third, the classification of PD patients according to patterns of regional cerebral perfusion was based on a hypothesis-driven rather than a data-driven approach. Finally, this was a single-center cohort with ethnic and regional homogeneity, which may limit the generalizability of the findings.

In conclusion, we demonstrated that occipital hypoperfusion on early-phase ^{18}F-FP-CIT PET images was not independently associated with an imminent risk of dementia conversion in PD patients, although patients with parieto-temporo-occipital hypoperfusion exhibited baseline clinical features resembling a diffuse malignant subtype. These findings may contribute to refining phenotype-based prognostic frameworks for patients with PD.

Supplementary Materials

The Data Supplement is available with this article at https://doi.org/10.14802/jmd.25231.

Conflicts of Interest

The authors have no financial conflicts of interest.

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