Association between striatal amyloid deposition and motor prognosis in Parkinson's disease

Mincheol Park

Department of Medicine

The Graduate School, Yonsei University

Association between striatal amyloid deposition and motor prognosis in Parkinson's disease

Directed by Professor Phil Hyu Lee

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Mincheol Park

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This certifies that the Master's Thesis of
Mincheol Park is approved.

[Signature]

Thesis Supervisor : Phil Hyu Lee

[Signature]

Thesis Committee Member#1 : Young H. Sohn

[Signature]

Thesis Committee Member#2 : Mijin Yun

[Signature]

Thesis Committee Member#3:

[Signature]

Thesis Committee Member#4:

[three signatures total in case of Master's]

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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The Graduate School, Yonsei University

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The co-occurrence of amyloid-β pathology in Parkinson's disease (PD) is common; however, the role of amyloid-β deposition in motor prognosis remains elusive. This study aimed to investigate the association between striatal amyloid deposition, motor complications, and motor prognosis in patients with PD. We retrospectively assessed 96 patients with PD who underwent F-18 florbetaben (FBB) PET. The ratio of the striatum to global (STG) FBB uptake was obtained for each individual, and patients were allotted into low and high STG groups according to the median value. We investigated the effect of STG group on regional amyloid deposition, the occurrence of motor complications, and longitudinal change in levodopa equivalent dose (LED) requirement after controlling for age, sex, LED, and disease duration at FBB scan. The high STG group was associated with lower cortical FBB uptake in the parietal, occipital, and posterior cingulate cortices and higher striatal FBB uptake compared to the low STG group. Patients in the high STG group had a higher risk of developing wearing-off and levodopa-induced dyskinesia than those in the low STG group, whereas the risk for freezing of gait was comparable between the two groups. The high STG group showed a more rapid increase in LED requirements over time than the low STG group. These findings suggest that relatively high striatal amyloid deposition is associated with poor motor outcomes in patients with PD.

Key words: Parkinson’s disease; amyloid-β; striatum; motor prognosis; motor complication

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I INTRODUCTION

Parkinson's disease (PD), a common neurodegenerative disease, exhibits relentless progression of pathological processes involving both the nigral and extra-nigral systems. Most patients with PD suffer from a progressive worsening of motor deficits and motor complications of wearing-off (WO), levodopa-induced dyskinesia (LID), and freezing of gait (FoG).[1-3] These motor complications can occur within the early course of the disease, impacting the quality of life and influencing treatment decisions.[1,2,4] Several factors such as age at diagnosis, age at symptom onset, sex, low body weight, initial motor subtype, low mood, anxiety, and cumulative exposure to levodopa have been shown to be associated with motor complications.[1,3,5]

Deposition of amyloid, one of the characteristic neuropathological marker of Alzheimer's disease (AD), is frequently observed in patients with PD. Neuropathological studies reported that amyloid deposition was observed in up to 50% of patients with PD,[6,7] and in vivo biomarker studies have revealed significant amyloid burden in up to 40% of patients with PD.[8,9] Several imaging and neuropathological studies of comorbid amyloid in PD have investigated the impact of amyloid on cognitive impairment,[8-10] focusing on cortical or global amyloid with the hypothesis of amyloid sequence that striatal amyloid deposition

occurs invariably after neocortical amyloid accumulation in AD.[11] Some studies additionally point to the role of striatal amyloid deposition in the development of cognitive impairment in PD.[9,12] However, the sequence and pattern of amyloid deposition in PD are supposed to be identical to those in AD, and have not been thoroughly investigated. Moreover, recent studies revealed that there may exist different sequences of amyloid accumulation between late-onset and genetic AD.[13,14]

Regarding the role of amyloid in the motor aspect of PD, one imaging study investigated the association between amyloid and motor phenotype.[15] However, the pattern of amyloid deposition and its association with the longitudinal motor prognosis in PD has not been investigated so far. Regarding the striatum as a hub of motor control, we hypothesized that striatal amyloid could influence motor prognosis in PD. Considering the possibility of heterogeneous pattern of amyloid deposition in PD, we hypothesized that the ratio of striatal to global amyloid deposition would reflect the relative abundance and earlier sequence of striatal amyloid accumulation. Thus, we investigated whether relative striatal amyloid deposition is associated with more frequent development of WO, LID, and FoG, as well as with worsening of motor deficits measured by levodopa-equivalent dose (LED) increments in patients with PD.

II MATERIALS AND METHODS

1. Participants

This was a retrospective cohort study of 96 patients with PD who visited the movement disorder outpatient clinic at Yonsei University Severance Hospital. We reviewed the medical records of patients who underwent F-18 florbetaben-PET (FBB-PET) for the

evaluation of cognitive decline from January 2015 to January 2022 at Severance Hospital. PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank.

We included patients who had a follow-up duration of at least 3 years after the diagnosis of PD to determine the occurrence of motor complications as much as possible. None of the participants had atypical parkinsonian features (e.g., poor response to dopaminergic medications, ataxia, prominent dysautonomia, vertical gaze impairment, early fall, or cortical sensory loss). Of 108 patients who underwent FBB-PET, 12 were excluded due to a follow-up duration of less than 36 months. Parkinsonism severity was assessed using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) at the initial visit. Olfactory function was assessed using the Cross-Cultural Smell Identification Test (CCSIT), and doses of PD medication were calculated as LEDs.[16] The presence of rapid eye movement sleep behavior disorder (RBD) and visual hallucinations were investigated by careful history taking and a semi-structured questionnaire during the visit and neuropsychiatric assessment. The study was approved by the Institutional Review Board of Severance Hospital (no. 4-2016-0210), and the requirement for informed consent was waived due to the retrospective chart review nature of the study.

2. Assessment of motor prognosis and dementia conversion

Following the first visit, the patients visited the outpatient clinic every 3 months. Two movement disorder specialists (Y.H.S. and P.H.L.) assessed the development of WO,[17]

LID,[18] and FoG[19] and adjusted the dose of PD medication for effective control of parkinsonian symptoms at every visit. The presence of LID was carefully assessed through the history from the patients and caregivers or by direct inspection. The onset of WO was defined as the time when either the patient first complained of deterioration at the end of the dose or when two movement disorder specialists first decided to increase the levodopa dosing schedule from three to four times a day. The FoG was defined as an unintentional and temporary phenomenon in which the feet failed to progress forward despite an intention to walk. Two movement disorder specialists inspected the patients' gait and specifically asked the patients about the characteristic sensation of their feet becoming "glued to the floor" at every visit. The first documented clinical visit date was regarded as the onset of each motor complication, and the latency of each motor complication was estimated from symptom onset. During the follow-up duration, a diagnosis of PD dementia was made by achieving consensus between 2 neurologists and 1 neuropsychologist, according to the clinical diagnostic criteria proposed by the Movement Disorder Society Task Force.[20]

3. Acquisition and interpretation of FBB-PET

FBB-PET was performed using Discovery 600 (General Electric Healthcare, Milwaukee, MI, USA). The detailed methods for FBB-PET acquisition have been described in a previous study.[21] Quantitative PET image processing method is almost identical to the Alzheimer's Disease Neuroimaging Initiative florbetaben PET processing performed by UC Berkeley[22] except that we used a PET template.[23] PET template was built on the Nathan Kline Institute brain template space using T1-weighted MRI and FBB-PET paired images of 454 healthy controls. Transformation between the PET template and each FBB-PET

image enables the definition of 68 cortical and 10 subcortical regions of the Desikan-Killiany Atlas[24] on the patient-specific space because the PET template holds a parcellation mask.

Standardized uptake value ratios (SUVRs) were calculated for four predefined cortical regions of interest (ROIs; frontal, temporal, parietal, and occipital lobes) and the striatum by overlaying the participant-specific composite masks. The whole cerebellum was used as a reference region. Additionally, global SUVRs were established for each participant by volume-weighted averaging across the frontal, lateral temporal, lateral parietal, and anterior/posterior cingulate regions, and dividing this by the reference region. Patients with composite amyloid retention above the threshold for amyloid positivity (global SUVRs > 1.20) were regarded as β-amyloid-positive.[25]

4. Classification of patients with PD according to the striatum to global ratio

Because of the heterogeneity of the timing of the FBB-PET scan, the total amount of amyloid deposition might have influenced regional amyloid deposition differently among participants. Assuming non-uniform sequence of amyloid deposition, we sought to reveal whether there exists a distinctive pattern of amyloid deposition regarding the relative burden of striatal amyloid to neocortical amyloid. Therefore, we used the ratio of the striatum to global (STG) amyloid deposition as the relative burden of striatal SUVR to global SUVR (striatal SUVR / global SUVR). Thereafter, patients were allocated into the

low and high STG groups, according to the median value of STG.

5. Acquisition and interpretation of FP-CIT

Dopamine transporter (DAT) imaging were quantitatively analyzed in those who had available DAT scan. Brain CT and 18F-FP-CIT PET images were acquired using a GE PET-CT DSTe scanner (GE Discovery STE; GE Healthcare, Milwaukee, WI, USA). Detailed methods for 18F-FP-CIT PET acquisition have been described in a previous study.[18] We used statistical parametric mapping 12 (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK) and in-house software implemented in MATLAB R2021a (MathWorks, Natick, MA, USA) for the simple arithmetic operation of images and measuring regional uptake values. Using CT and MR image data from 71 healthy controls, we created skull-stripped CT (ssCT) templates for 18F-FP-CIT PET analyses. Spatially normalized 18F-FP-CIT PET images were obtained using the ssCT-guided spatial normalization method. To measure striatal and cerebellar binding values in spatially normalized PET images, we created volume-of-interest (VOI) templates for the caudate, putamen, and cerebellum. The striatal and cerebellar segments were obtained by subcortical parcellation using FreeSurfer. Using the VOI template, we measured the regional SUV values of the cerebellum and each side of the caudate and putamen in the PET images. The mean SUVR values of both sides of the caudate and putamen were calculated as follows: SUVR target = SUVtarget / SUVcerebellum. The detailed image-processing steps for acquiring the ssCT template are described in our previous paper.[26]

6. Statistical analysis

Statistical analyses were performed using SPSS (version 26.0; IBM Corporation, Armonk, NY). Baseline clinical characteristics were compared between the low and high STG groups using chi-square and independent t-tests. The effects of the STG group on regional amyloid deposition were investigated using multivariate linear regression analysis, considering the age at FBB-PET and sex as covariates. We used Kaplan-Meier method to estimate the cumulative incidence of WO, LID, and FoG. Cox regression analyses were conducted to compare the WO-, LID-, and FoG-free time between the two groups while adjusting for age, disease duration and LED at FBB-PET, and sex as covariates. The association between STG group and long-term motor outcomes was assessed using a linear mixed model for the longitudinal increases in LED over time. A linear mixed model was used to compare the rates of the longitudinal LED changes according to STG group. Participants were added as random effects and age at FBB-PET, sex, disease duration and LED at FBB-PET as fixed effects. We considered time as a continuous variable. The effect of STG group on longitudinal changes in LED was tested using a STG group × Time interaction term. A false discovery rate-controlling method was used for multiple comparisons, and a p-value and corrected Q value < 0.05 was considered significant.

7. Sensitivity analysis

As DAT imaging was available in 76 participants, we performed sensitivity analyses including putaminal DAT uptake as an additional covariate in each analysis. We used Cox regression models to compare WO-, LID-, and FoG-free time between groups while

adjusting for age, disease duration and LED at FBB-PET, sex, and putaminal DAT availability. A linear mixed model was used to compare the rates of longitudinal increases in LED between the groups, further controlling for putaminal DAT availability as an additional fixed effect.

III RESULTS

1. Baseline characteristics

The demographic characteristics of the patients in the high- and low-STG groups are summarized in Table 1. Median STG in overall patients was 0.97, and the mean STG was 1.05 and 0.89 in the high STG group and low STG group, respectively. Patients in the high STG group had earlier symptom onset and lower age at FBB-PET acquisition and a higher proportion of male patients compared to those in the low STG group. The total follow-up duration, disease duration and LED at FBB-PET acquisition, initial UPDRS part III score, CCSIT score, and proportion of patients with RBD and visual hallucinations were comparable between the two groups. During follow-up, patients in the higher STG group had more frequent WO (39.6% vs. 16.7%, $p = 0.013$) and LID (35.4% vs. 12.5%, $p = 0.009$) than those in the lower STG group, but the development of FoG and dementia was comparable between the two groups. The proportion of patients with β-amyloid positivity was higher in the low STG group. The sensitivity analysis of the subgroup of 76 patients whose baseline DAT data were available is shown in Table 2. The patients had similar demographic characteristics to all enrolled patients, and putaminal DAT availability did not differ between the groups.

Table 1. Baseline characteristics of participants in the study

	Total group	Low STG group	High STG group	p-value
Number of patients	96	48	48	
Age at symptom onset, years	69.2 ± 9.9	71.9 ± 8.0	66.4 ± 10.8	0.005
Sex, male (%)	58 (60.4)	23 (47.9)	35 (72.9)	0.012
Follow-up duration, months	58.4 ± 38.2	52.8 ± 30.7	63.9 ± 44.1	0.156
Age at FBB-PET, years	74.2 ± 8.4	76.4 ± 6.3	71.9 ± 9.6	0.009
Interval from the diagnosis to FBB-PET, months	60.6 ± 44.5	53.8 ± 42.2	67.5 ± 46.2	0.131
LED at FBB-PET, mg	508.4 ± 375.8	461.7 ± 334.3	555.1 ± 411.4	0.225
Initial UPDRS	22.6 ± 8.7	21.5 ± 8.2	23.6 ± 9.1	0.260
CCSIT	6.0 ± 2.6	6.1 ± 3.1	5.9 ± 2.2	0.714
RBD, N (%)	60 (62.5)	28 (58.3)	32 (66.7)	0.399
Visual hallucination, N (%)	54 (56.3)	26 (57.8)	28 (62.2)	0.667
WO, N (%)	27 (28.1)	8 (16.7)	19 (39.6)	0.013
LID, N (%)	23 (24.0)	6 (12.5)	17 (35.4)	0.009
FoG, N (%)	13 (13.5)	4 (8.3)	9 (18.8)	0.136
Dementia conversion, N (%)	71 (74.0)	36 (75.0)	35 (72.9)	0.816
Amyloid positivity, N (%)	21 (21.9)	15 (31.3)	6 (12.5)	0.026
STG value	0.97 (0.10)	0.89 (0.07)	1.05 (0.04)	< 0.001

Data are expressed as mean ± standard deviation or number (percentage). Group comparisons were performed using the chi-square test or independent t-test, as appropriate. Abbreviations: CCSIT, cross-cultural smell identification test; FBB-PET, ^{18}F-florbetaben positron emission tomography; FoG, freezing of gait; LED, levodopa equivalent dose; LID,

levodopa-induced dyskinesia; RBD, rapid eye movement sleep behavior disorder; STG, striatum-to-global ratio; UPDRS, Unified Parkinson's Disease Rating Scale; WO, wearing-off.

Table 2. Baseline characteristics of participants with available DAT scans

	Total group	Low STG group	High STG group	p-value
Number of patients	76	38	38	
Age at symptom onset	69.5 ± 10.4	72.1 ± 8.7	67.0 ± 11.4	0.032
Sex, male (%)	47 (61.8)	20 (52.6)	27 (71.1)	0.098
Follow-up duration, months	61.9 ± 35.4	57.5 ± 30.3	66.3 ± 39.8	0.283
Age at FBB-PET	74.2 ± 8.9	76.4 ± 6.7	72.1 ± 10.4	0.034
Interval from the diagnosis to FBB-PET	57.1 ± 44.4	52.5 ± 45.9	61.7 ± 43.0	0.368
LED at FBB-PET	466.4 ± 368.2	407.7 ± 295.2	525.1 ± 425.0	0.166
Initial UPDRS	21.5 ± 8.8	20.4 ± 8.3	22.6 ± 9.2	0.310
CCSIT	6.0 ± 2.6	6.2 ± 3.0	5.9 ± 2.3	0.654
RBD, N (%)	48 (63.2)	23 (60.5)	25 (65.8)	0.634
Visual hallucination, N (%)	45 (59.2)	22 (57.9)	23 (60.5)	0.815
WO, N (%)	18 (23.7)	4 (10.5)	14 (36.8)	0.007
LID, N (%)	15 (19.7)	3 (7.9)	12 (31.6)	0.009
FoG, N (%)	9 (11.8)	4 (10.5)	5 (13.2)	0.723

Dementia conversion, N (%)	52 (68.4)	26 (68.4)	26 (68.4)	1.000
Amyloid positivity, N (%)	18 (23.7)	12 (31.6)	6 (15.8)	0.105
STG value	0.97 ± 0.09	0.90 ± 0.06	1.05 ± 0.04	< 0.001
Putaminal DAT availability	3.60 ± 1.09	3.84 ± 1.36	3.36 ± 0.65	0.059

Data are expressed as mean ± standard deviation or number (percentage). Group comparisons were performed using the chi-square test or independent t-test, as appropriate. Abbreviations: CCSIT, cross-cultural smell identification test; FBB-PET, 18F-florbetaben positron emission tomography; FoG, freezing of gait; LED, levodopa equivalent dose; LID, levodopa-induced dyskinesia; RBD, rapid eye movement sleep behavior disorder; STG, striatum-to-global ratio; UPDRS, Unified Parkinson's Disease Rating Scale; WO, wearing-off.

2. Regional amyloid deposition between the high and low STG groups

The high STG group was associated with lower FBB uptake in the parietal (standardized beta [β] = -0.08; p = 0.011; Q = 0.036), occipital (β = -0.07; p = 0.018; Q = 0.036), and posterior cingulate cortex (β = -0.10; p = 0.017; Q = 0.036) compared to the low STG group (Figure 1, Table 3). The high STG group was associated with higher FBB uptake in the striatum (β = 0.10, p = 0.001, Q = 0.008) relative to the low STG group. However, the STG group was not associated with global FBB uptake (β = -0.06; p = 0.050; Q = 0.067).

Table 3. Effect of the high STG group on regional amyloid deposition

	β (SE)	p-value	Q-value
Frontal cortex	-0.06 (0.03)	0.045	0.067
Parietal cortex	-0.08 (0.03)	0.011	0.036
Temporal cortex	-0.04 (0.03)	0.231	0.231
Occipital cortex	-0.07 (0.03)	0.018	0.036
Anterior cingulate cortex	0.05 (0.04)	0.193	0.221
Posterior cingulate cortex	-0.10 (0.04)	0.017	0.036
Striatum	0.10 (0.03)	0.001	0.008
Global	-0.06 (0.03)	0.050	0.067

Data are the results of multivariate linear regression models for regional SUVR values after controlling for age at the FBB scan and sex as covariates. The predictor was the STG group, and the low STG group was considered as a reference.

Q-values are corrected p-values for multiple comparisons using the false discovery rate method.

Abbreviations: SE, standard error; STG, striatum-to-global ratio; SUVR, standardized uptake value ratio.

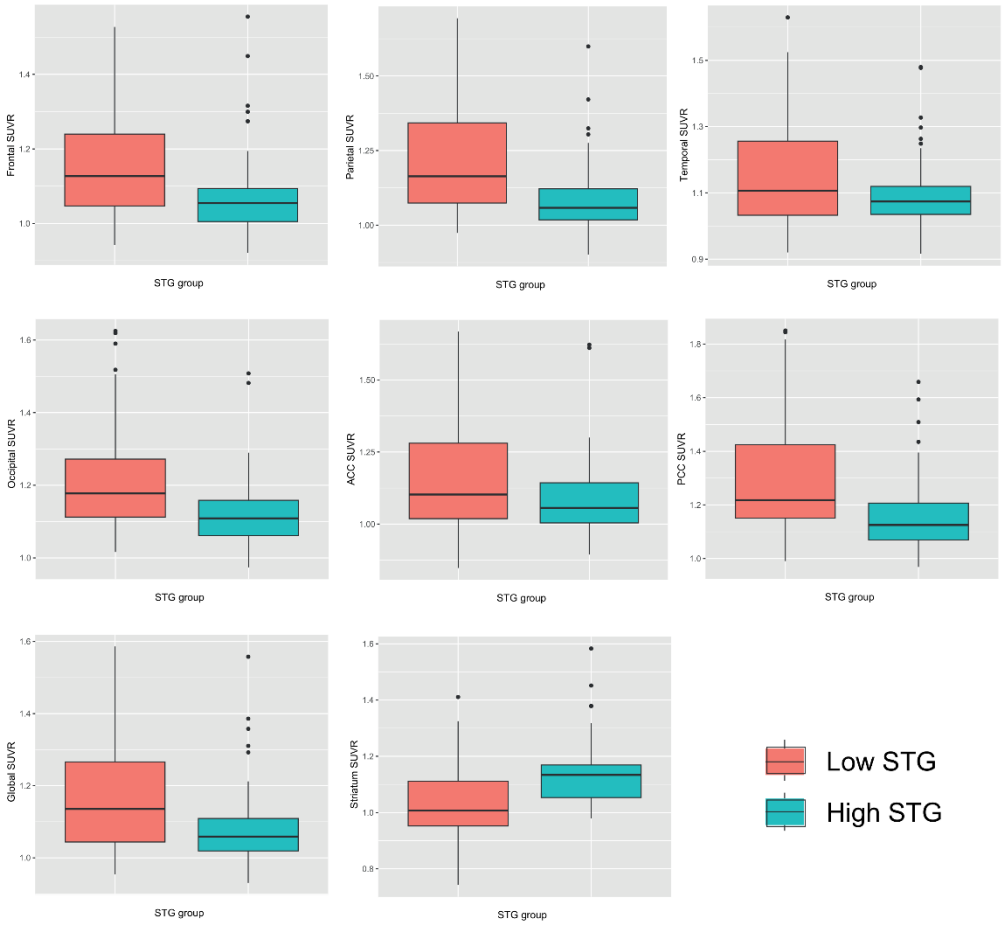


Figure 1. Box-and-whisker plots of regional SUVR according to the STG group. Patients in the high STG group showed lower regional SUVR in the parietal, occipital, and posterior cingulate cortices and higher regional SUVR in the striatum.

Abbreviations: ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; STG, striatum to global ratio; SUVR, standardized uptake value ratio.

3. Development of wearing off between the high and low STG groups

During the follow-up period (52.8 ± 30.7 months in the low STG group and 63.9 ± 44.1 months in the high STG group), WO developed in 8 (16.7%) patients in the low STG group and 19 (39.6%) patients in the high STG group. Kaplan–Meier analysis revealed that the high STG group had a higher risk of developing WO than the low STG group (Plog-rank = 0.038, Figure 2). After adjusting covariates, the Cox regression model revealed that the high STG group had a higher risk of developing WO (hazard ratio [HR], 3.36; 95% confidence interval [CI], 1.24 – 9.11; p = 0.017; Table 4). Sensitivity analysis showed that the high STG group had a high risk of developing WO (HR, 4.92; 95% CI, 1.29 – 18.80; p = 0.020; Table 5)

4. Development of levodopa induced dyskinesia between the high and low STG groups

During the follow-up period, LID developed in 6 (12.5%) and 17 (35.4%) patients in the low STG and high STG groups, respectively. Kaplan-Meier analysis revealed that the high STG group had a higher risk of developing LID than the low STG group (Plog-rank = 0.021, Figure 2). After adjusting covariates, the Cox regression model revealed that the high STG group had a higher risk of developing LID (HR, 5.48; 95% CI, 1.66 – 18.05; p = 0.005; Table 4). Sensitivity analysis showed that the high STG group had a high risk of developing LID (HR, 10.64; 95% CI, 1.77 – 63.93; p = 0.010; Table 5).

5. Development of freezing of gait between the high and low STG groups

During the follow-up period, FoG developed in 4 (8.3%) and 9 (18.8%) patients in the low STG and high STG groups, respectively. Kaplan–Meier analysis revealed that the high and low STG groups had a comparable risk of developing FoG (Plog-rank = 0.241, Figure 2). The Cox regression model revealed that the risk of developing FoG was comparable between the high- and low-STG groups (HR, 0.71; 95% CI, 0.17 – 3.07; p = 0.648; Table 4). Similarly, sensitivity analysis showed no significant difference in FoG development between the groups (HR, 0.29; 95% CI, 0.04 – 2.05; p = 0.212; Table 5).

Table 4. Cox regression analyses of motor complications according to the STG group

	Hazard ratio (95% CI)	p-value
Wearing off		
Age at FBB-PET	0.966 (0.924 – 1.009)	0.121
Sex, female	2.493 (1.039 – 5.986)	0.041

Disease duration at FBB-PET	0.980 (0.965 – 0.995)	0.009
LED at FBB-PET	1.002 (1.001 – 1.003)	0.005
High STG group	3.36 (1.241 – 9.108)	0.017
Levodopa-induced dyskinesia		
Age at FBB-PET	1.011 (0.962 – 1.063)	0.668
Sex, female	3.389 (1.215 – 9.450)	0.020
Disease duration at FBB-PET	0.977 (0.960 – 0.993)	0.005
LED at FBB-PET	1.003 (1.001 – 1.004)	< 0.001
High STG group	5.480 (1.664 – 18.045)	0.005
Freezing of gait		
Age at FBB-PET	0.926 (0.860 – 0.998)	0.043
Sex, female	0.095 (0.013 – 0.720)	0.023
Disease duration at FBB-PET	0.968 (0.940 – 0.997)	0.030
LED at FBB-PET	1.003 (1.001 – 1.005)	0.013
High STG group	0.711 (0.165 – 3.070)	0.648

Cox regression analysis included the STG group as a predictor, with age at FBB-PET, sex, disease duration at FBB-PET, and LED at FBB-PET as covariates.

Abbreviations: CI, confidence interval; FBB-PET, ^{18}F-florbetaben positron emission tomography; LED, levodopa equivalent dose; STG, striatum-to-global ratio.

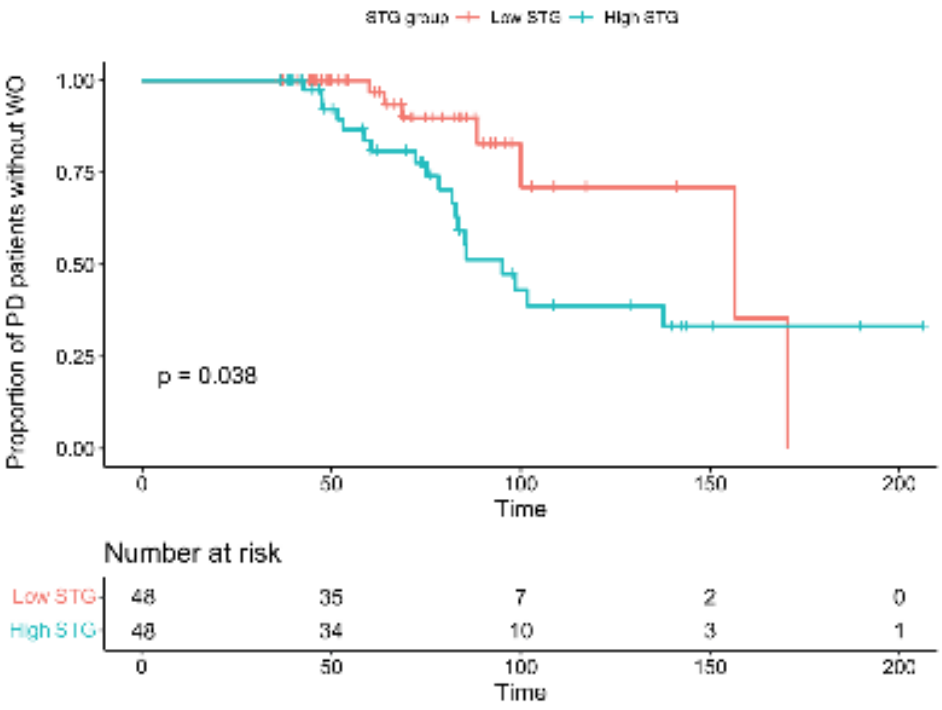
Table 5. Cox regression analyses of motor complications according to the STG group considering DAT availability

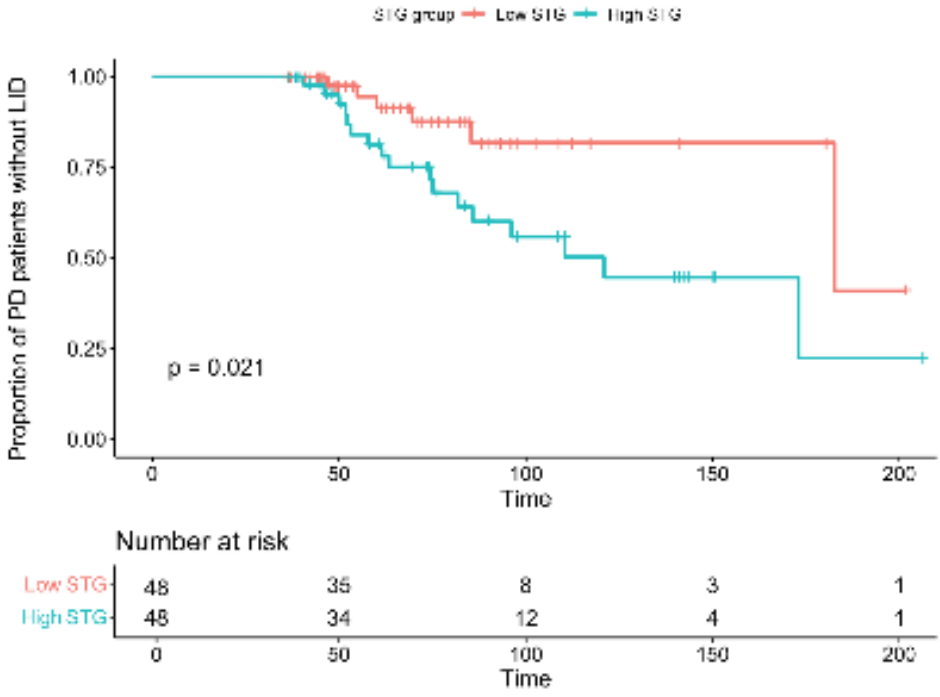
	Hazard ratio (95% CI)	p-value
Wearing off		
Age at FBB-PET	0.98 (0.92 – 1.03)	0.386

Sex, female	2.12 (0.67 – 6.70)	0.201
Disease duration at FBB-PET	0.97 (0.95 – 0.994)	0.014
LED at FBB-PET	1.002 (1.000 – 1.004)	0.016
Putaminal DAT availability	0.69 (0.33 – 1.47)	0.338
High STG group	4.92 (1.29 – 18.80)	0.020
Levodopa-induced dyskinesia		
Age at FBB-PET	1.01 (0.94 – 1.08)	0.844
Sex, female	3.07 (0.85 – 11.15)	0.088
Disease duration at FBB-PET	0.98 (0.95 – 0.998)	0.036
LED at FBB-PET	1.002 (1.001 – 1.004)	0.009
Putaminal DAT availability	1.16 (0.56 – 2.39)	0.695
High STG group	10.64 (1.77 – 63.93)	0.010
Freezing of gait		
Age at FBB-PET	0.90 (0.81 – 1.01)	0.067
Sex, female	0.01 (0.00 – 1.93)	0.082
Disease duration at FBB-PET	0.97 (0.94 – 1.01)	0.173
LED at FBB-PET	1.003 (1.000 – 1.005)	0.063
Putaminal DAT availability	0.36 (0.07 – 1.84)	0.217
High STG group	0.29 (0.04 – 2.05)	0.212

Cox regression analysis included the STG group as a predictor, with age at FBB-PET, sex, disease duration at FBB-PET, LED at FBB-PET, and putaminal DAT availability as covariates.

Abbreviations: CI, confidence interval; DAT, dopamine transporter; FBB-PET, 18F-florbetaben positron emission tomography; LED, levodopa equivalent dose; STG, striatum-to-global ratio.





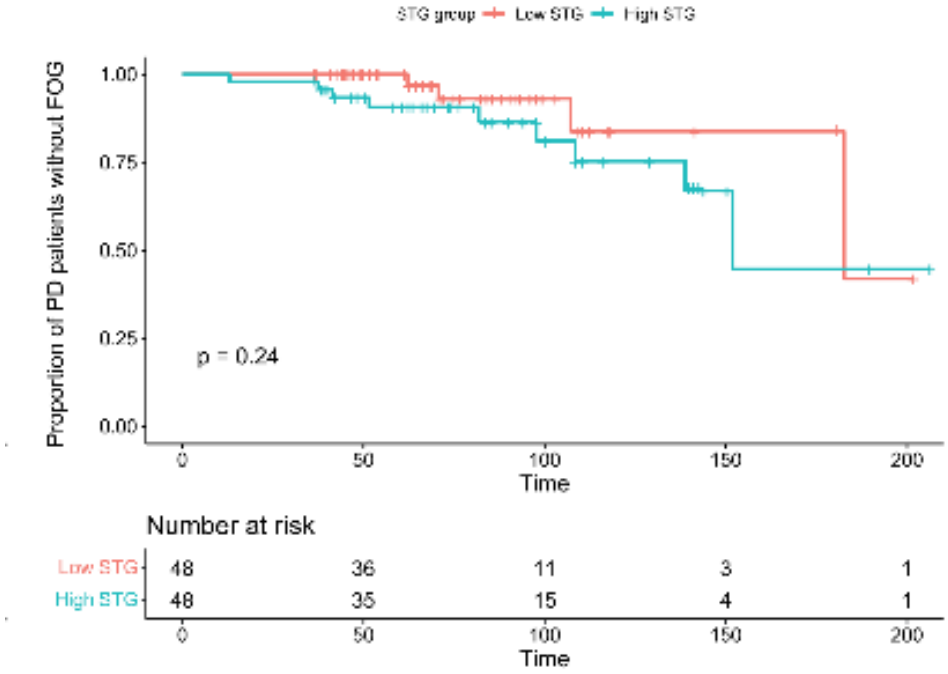


Figure 2. Kaplan-Meier survival curve of developing wearing-off, levodopa-induced dyskinesia, and freezing of gait. Curves of Kaplan-Meier estimates of developing WO, LID, and FoG after symptom onset in the high STG group (in green) and low STG group (in red). Patients in the high STG group showed a higher risk of WO and LID during the follow-up period. The risk of developing FoG was comparable between the two groups.
Abbreviations: FoG, freezing of gait; LID, levodopa-induced dyskinesia; PD, Parkinson's disease; STG, striatum to global ratio; WO, wearing-off.

6. Longitudinal assessment of the changes in levodopa equivalent doses between the groups

The STG group × Time interaction term in the linear mixed model was statistically significant ($\beta = 1.50$; standard error [SE] = 0.33; $p < 0.001$; Table 6, Figure 3) after adjusting for age at FBB-PET, sex, disease duration and LED at FBB-PET, STG group, time and STG group × time, indicating that high STG group needs 1.50 more LED monthly than the low STG group. Even when additionally controlling for putaminal DAT availability, the LED changes in the higher STG group were greater than those in the low STG group ($\beta = 1.72$; SE = 0.38; $p < 0.001$, Table 7). Information on anti-parkinsonian medications at the time of the FBB-PET scan is available in Table 8.

Table 6. Longitudinal changes in the levodopa equivalent dose according to the STG group

	β (SE)	p-value
Intercept	248.64 (230.90)	0.282
Group		
High STG	-109.08 (50.25)	0.030
Low STG	Reference	
Age at FBB-PET, years	-0.35 (2.94)	0.906
Sex		
Male	21.44 (48.23)	0.657
Female	Reference	
Disease duration at FBB-PET, months	-0.42 (0.66)	0.531
LED at FBB-PET	0.39 (0.08)	< 0.001
Time, months	5.04 (0.20)	< 0.001
Group (High STG) * Time	1.50 (0.33)	< 0.001
Group (Low STG) * Time	Reference	

Results of linear mixed models for LED after controlling for age at FBB-PET, sex, disease duration at FBB-PET, LED at FBB-PET, STG group, time, and STG group × time.

Abbreviations: FBB-PET, 18F-florbetaben positron emission tomography; LED, levodopa equivalent dose; SE, standard error; STG, striatum-to-global ratio.

Table 7. Longitudinal changes in the levodopa equivalent dose according to the STG group considering putaminal DAT availability

	Beta (SE)	p-value
Intercept	538.34 (232.25)	0.021
Group		
High STG	-107.84 (49.90)	0.031
Low STG	Reference	
Age at FBB-PET, years	-1.77 (3.03)	0.560
Sex		
Male	29.41 (50.08)	0.557
Female	Reference	
Disease duration at FBB-PET, months	0.33 (0.66)	0.614
LED at FBB-PET, mg	0.19 (0.08)	0.025
Putaminal DAT availability	-40.87 (23.68)	0.085
Time, months	5.15 (0.24)	< 0.001
Group * Time		
Group (High STG) * Time	1.72 (0.38)	< 0.001
Group (Low STG) * Time	Reference	

Results of linear mixed models for LED after controlling for age at FBB-PET, sex, disease duration at FBB-PET, LED at FBB-PET, putaminal DAT availability, STG group, time, and STG group × time.

Abbreviations: DAT, dopamine transporter; FBB-PET, 18F-florbetaben positron emission tomography; LED, levodopa equivalent dose; SE, standard error; STG, striatum-to-global ratio.

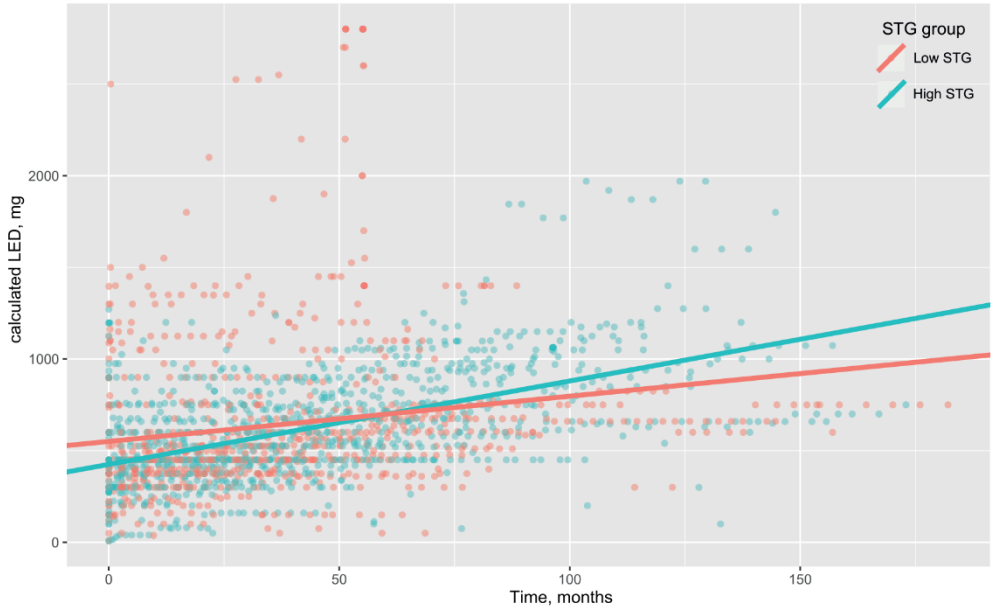


Figure 3. Association between STG group and levodopa equivalent doses over time. A linear mixed model analysis showed a significant difference between the high STG (in green) and low STG (in red) groups (STG group × Time interaction, $P < 0.001$).
Abbreviations: STG, striatum to global ratio.

Table 8. Anti-parkinsonian medication at the FBB-PET scan

	Total group	Low STG group	High STG group	p-value
Number of patients	96	48	48	
Levodopa	94 (97.9)	46 (95.8)	48 (100.0)	0.153
Dopamine agonist	42 (43.8)	18 (37.5)	24 (50.0)	0.217
COMT inhibitor	9 (9.4)	5 (10.4)	4 (8.3)	0.726
MAO inhibitor	9 (9.4)	1 (2.1)	8 (16.7)	0.014
Amantadine	4 (4.2)	2 (4.2)	2 (4.2)	1.000

Data are expressed as number (percentage). Group comparisons were performed using the chi-squared test.

Abbreviations: COMT, catechol-O-methyltransferase; FBB-PET, Florbetaben-positron emission tomography; MAO, monoamine oxidase; STG, striatal-to-global ratio.

IV DISCUSSION

Our study investigated the association between relative striatal amyloid deposition and long-term motor outcomes in patients with PD. The major findings were as follows: (1) the high STG group was associated with lower FBB uptake in the parietal, occipital, and posterior cingulate cortices and higher FBB uptake in the striatum; (2) patients in the high STG group had a higher risk of developing WO and LID throughout the follow-up period, while the risk for FoG was comparable between the two groups; and (3) patients in the high

STG group required higher doses of dopaminergic medications over time than those in the low STG group. These findings suggest that high STG is associated with poor motor outcomes in patients with PD.

Although amyloid deposition is often observed in patients with PD, the sequence and pattern of amyloid accumulation have not been studied thoroughly in PD. Classic amyloid deposition in patients with AD is thought to begin in the neocortex, spread into the allocortex, and then into the deep gray matter such as the striatum and thalamus, and finally extend into the cerebellum and brainstem.[27] However, a recent study revealed a possibility of several subtypes in the sequence of amyloid deposition in AD, demonstrating frontal, parietal, and occipital subtypes of cortical amyloid accumulation.[28] Moreover, patients with genetic predisposition have earlier and more prominent striatal amyloid deposition than neocortical amyloid deposition.[14,29] Therefore, it is plausible to assume that patients with PD might also have heterogeneous sequences of amyloid deposition, and that some patients with PD might exhibit early amyloid deposition in the striatum than the neocortex. However, the impact of striatal amyloid deposition in PD has been investigated in terms of regional positivity, judging positivity elicited from a normalized distribution derived from the control group.[9] Moreover, prior neuropathological study revealed more severe pathological amyloid burden in the striatum compared to the neocortex in demented PD.[12] In the present study, we used the relative burden of striatal amyloid over the global amyloid deposition, dividing participants into high and low STG groups. The high STG group was associated with lower cortical FBB uptake and higher caudate FBB uptake after correcting for the effects of age and sex. This is quite similar to the pattern observed in autosomal dominant AD and Down syndrome patients.[14,30] Therefore, higher STG group would reflect a distinct pattern of amyloid deposition, in which amyloid accumulates in the striatum in the earlier phase, and our finding suggests that some patients with PD may have striatal amyloid deposition in the earlier phase of the temporal trajectory. In addition, comparable global amyloid burden between the high and low STG groups in our study may also support

this assumption. Generally, aging is a main contributor of amyloidosis in AD or other neurodegenerative diseases:[31] however, the present study showed that the high STG group showed younger age at FBB-PET scan, compared to the low STG groups. Accordingly, it is possible that PD patients with higher striatal amyloid deposition may be a unique disease group entity, possibly having a certain genetic predisposition.

Interestingly, we found that higher STG group was associated with a higher risk of developing WO and LID. WO and LID are presumed to share some common pathophysiological mechanism: both presynaptic dopaminergic depletion and postsynaptic mechanisms involving dopaminergic receptor modification or alterations in striatocortical networks are thought to be associated with the development of WO and LID.[32-35] In our study, sensitivity analyses revealed that relative striatal amyloid deposition was independently associated with the risk of WO and LID development after controlling for putaminal DAT availability. Therefore, our data suggest that the vulnerability to WO and LID in the high STG group may be ascribed to postsynaptic mechanisms. With regard to the possible mechanism, it is plausible that the increased burden of striatal amyloid may be associated with alterations in postsynaptic striatal neurons, resulting in a decreased threshold of motor complications; however, the absolute SUVR of striatal amyloid was not associated with the development of motor complications (data not shown). Rather, the higher STG group may be a subpopulation of patients with PD representing another predisposing factor for motor complications, even though the underlying pathophysiology is unknown. Considering possible interaction between α-synuclein and amyloid-β, high STG may imply its interaction at the striatum.[36] However, further clinical studies with genetic and neuropathological examinations are warranted to unveil this issue. In terms of FoG, unlike a biomarker study showing that amyloid burden in cerebrospinal fluid is closely related to FoG,[37] our data revealed no association between amyloid burden and FoG. Several non-dopaminergic neural correlates, such as limbic system or complex gait-associated subcortical and cortical areas, would contribute to the development of FoG,[38]

and thus, a relative striatal amyloid load may not affect the incidence of FoG in this study.

In terms of prognosis of motor deficits, the high STG group showed more rapid increases in the doses of PD medications than the low STG group throughout the follow-up period, even though the baseline motor deficits were comparable between the groups. This may be partially attributable to the poor response to dopaminergic medications in the high STG group. Alternatively, this finding also suggests that pathological conditions related to high relative striatal amyloid deposition might be associated with the progression of motor disability in patients with PD. Since many pathological conditions of nigral and extra-nigral areas,[39,40] as well as genetic factors[41] would affect the longitudinal prognosis of motor deficits, PD patients with high STG may be prone to have faster increment in LED required to maintain favorable motor symptoms against the progression of PD-associated pathology.

Our study has some limitations. First, the timing of the FBB scan acquisition was not uniform. As the design of this study was retrospective, FBB-PET scans were acquired as needed during the clinical follow-up period. However, in order to compensate for the different timing of the FBB-PET scan along the disease course, we adopted the STG ratio to investigate the relative abundance of striatal amyloid in each participant. Second, we divided the patients into two groups (high STG vs. low STG). As this is the first study investigating the relative accumulation between striatal and global amyloid in PD, how to distinguish between high and low striatal amyloid deposition in PD needs to be investigated in future studies. Third, DAT imaging was not available for all participants, and the time gap between DAT imaging and FBB-PET varied. However, we performed additional sensitivity analyses controlling for putaminal DAT availability for participants whose DAT imaging were available, revealing similar results to those without controlling putaminal DAT availability. Moreover, the baseline UPDRS part III score, and disease duration and LED at FBB-PET scans were comparable between the high and low STG groups.

V CONCLUSION

In conclusion, our study demonstrated that higher STG was associated with lower cortical amyloid deposition and higher striatal amyloid deposition, a higher risk of developing WO and LID, and more rapid increases in the doses of PD medications. These findings suggest that relatively high striatal amyloid deposition, which can be acquired in vivo by PET imaging, may serve as a marker for motor prognosis in patients with PD.

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ABSTRACT(IN KOREAN)

선조체 아밀로이드 침착이 파킨슨병의 운동 예후에 미치는 영향

<지도교수 이 필 휴>

연세대학교 대학원 의학과

박 민 철

파킨슨병에서 베타-아밀로이드 병리의 동반은 흔하게 발견된다. 하지만, 베타-아밀로이드의 침착이 파킨슨병의 운동 예후에 있어서 미치는 영향에 대해서는 잘 연구되어있지 않다. 본 연구에서는 파킨슨 병에서 선조체의 아밀로이드 침착과 운동합병증, 운동 예후와의 연관성에 대해 연구를 진행하였다. 96명의 플로르베타벤 양전자 단층촬영영상을 시행한 파킨슨병 환자를 대상으로 하여 선조체-전체비 (striatum to global ratio, STG)를 통하여 높은 STG 군과 낮은 STG 군으로 분류 후, 연령, 성별, 추적시 레보도파 동등용량, 질병이환기간을 보정변수로 하여 STG 군에 따른 부위별 아밀로이드 침착, 운동합병증의 발생, 레보도파 동등용량의 변화를 비교하였다. 높은 STG 군에서 더 낮은 두정엽, 후두엽, 후측대상피질의 플로르베타벤 섭취와 더 높은 선조체 플로르베타벤 섭취를 보였다. 높은 STG군은 약물소진과 레보도파 유발 이상운동증의 위험이 낮은 STG군에 비교하여 더 높았으며, 보행동결의 위험은 두 군에서 차이가 없었다. 높은 STG군에서 추적기간동안 시간에 따른 레보도파 동등용량의 증가율이 더 높았다. 이런 결과들은 선조체 아밀로이드의 침착이 파킨슨병에서의 불량한 운동예후와 연관이 있음을 시사한다.

핵심되는 말: 파킨슨병; 베타-아밀로이드; 선조체; 운동예후; 운동합병증