

ORIGINAL ARTICLE

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

Mincheol Park^{1,2}  | Hyun Joo Kim³ | Kyoungwon Baik⁴ | Han Kyu Na¹ |
Young-gun Lee^{1,5}  | So Hoon Yoon^{1,6}  | Seong Ho Jeong⁷  | Seok Jong Chung¹  |
Hae-Won Shin⁸  | Chul Hyung Lyoo^{1,9}  | Young H. Sohn¹ | Phil Hyu Lee¹

¹Department of Neurology, Yonsei University College of Medicine, Seoul, Republic of Korea

²Department of Neurology, Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong, Republic of Korea

³Department of Nuclear Medicine, Korea University Anam Hospital, Seoul, Republic of Korea

⁴Department of Neurology, Korea University Anam Hospital, Seoul, Republic of Korea

⁵Department of Neurology, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea

⁶Department of Neurology, Catholic Kwandong University International St. Mary's Hospital, Incheon, Republic of Korea

⁷Department of Neurology, Inje University Sanggye Paik Hospital, Seoul, Republic of Korea

⁸Department of Neurology, Chung-Ang University College of Medicine, Seoul, Republic of Korea

⁹Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Correspondence

Phil Hyu Lee, Department of Neurology,
Yonsei University College of Medicine, 50
Yonsei-ro, Seodaemun-gu, Seoul 03722,
Republic of Korea.
Email: phlee@yuhs.ac

Funding information

Korea Health Industry Development
Institute, Grant/Award Number:
HU21C0053

Abstract

Background and purpose: 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.

Methods: Ninety-six patients with PD who underwent ¹⁸F florbetaben (FBB) positron emission tomography were retrospectively assessed. 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. The effect of STG group on regional amyloid deposition, the occurrence of motor complications and longitudinal change in levodopa equivalent dose (LED) requirement were investigated after controlling for age, sex, LED and disease duration at FBB scan.

Results: 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.

Mincheol Park and Hyun Joo Kim contributed equally to this work.

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Conclusions: These findings suggest that relatively high striatal amyloid deposition is associated with poor motor outcomes in patients with PD.

KEYWORDS

amyloid- β , motor complication, motor prognosis, Parkinson disease, striatum

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 markers 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 have not been investigated so far. Regarding the striatum as a hub of motor control, it was hypothesized that striatal amyloid could influence motor prognosis in PD. Considering the possibility of a heterogeneous pattern of amyloid deposition in PD, it was 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.

METHODS

Participants

This was a retrospective cohort study of 96 patients with PD who visited the movement disorder outpatient clinic at Yonsei University Severance Hospital. The medical records of patients who underwent ^{18}F florbetaben positron emission tomography (FBB-PET) for the evaluation of cognitive decline from January 2015 to January 2022 at Severance Hospital were reviewed. PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank.

Patients who had a follow-up duration of at least 3 years after the diagnosis of PD were included 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 behaviour disorder (RBD) and visual hallucinations was investigated by careful history taking, a semi-structured questionnaire during the visit and neuropsychiatric assessment.

Standard protocol approvals, registrations and patient consents

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.

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 two neurologists and one neuropsychologist, according to the clinical diagnostic criteria proposed by the Movement Disorder Society Task Force [20].

Acquisition and interpretation of FBB-PET

^{18}F florbetaben 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]. The 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 a PET template was used [23]. The PET template was built on the Nathan Kline Institute brain template space using T1-weighted magnetic resonance imaging and FBB-PET paired images of 454 healthy controls. Transformation between the PET template and each FBB-PET image enabled 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 (frontal, temporal, parietal and occipital lobes) and the striatum by overlying 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 [22].

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 amongst participants. Assuming a non-uniform sequence of amyloid deposition, it was sought to reveal whether there exists a distinctive pattern of amyloid deposition regarding the relative burden of striatal amyloid to neocortical amyloid.

Therefore, the ratio of the striatum to global (STG) amyloid deposition was used 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.

Statistical analysis

Statistical analyses were performed using SPSS (version 26.0; IBM Corporation, Armonk, NY, USA). Baseline clinical characteristics were compared between the low and high STG groups using chi-squared 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. The Kaplan–Meier method was used 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 whilst adjusting for age, disease duration at FBB-PET, 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 included as random effects, while age at FBB-PET, sex, disease duration at FBB-PET and LED at FBB-PET were included as fixed effects. Time was considered as a continuous variable. The effect of STG group on longitudinal changes in LED was tested using an STG group $\times$ time interaction term. A false discovery rate controlling method was used for multiple comparisons, and a *p* value and corrected *Q* value <0.05 were considered significant.

Sensitivity analyses

As dopamine transporter (DAT) imaging was available in 76 participants, sensitivity analyses were performed including putaminal DAT uptake derived from *N*-(3-fluoropropyl)-2 β -carboxymethoxy-3 β -(4-iodophenyl) nortropane (FP-CIT) PET as an additional covariate in each analysis. The detailed process for acquiring and interpretation of FP-CIT and sensitivity analyses are described in Supplementary Methods in Appendix S1.

RESULTS

Baseline characteristics

The demographic characteristics of the patients in the high and low STG groups are summarized in Table 1. Median STG in patients overall 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

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

Note: Data are expressed as mean ± standard deviation or number (percentage). Group comparisons were performed using the chi-squared 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 behaviour disorder; STG, striatum to global ratio; UPDRS, Unified Parkinson's Disease Rating Scale; WO, wearing off.

the low STG group. The total follow-up duration, disease duration at FBB-PET acquisition, LED at FBB-PET acquisition, initial UPDRS-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 S1](#). The patients had similar demographic characteristics to all enrolled patients, and putaminal DAT availability did not differ between the groups.

Regional amyloid deposition between the high and low STG groups

The high STG group was associated with lower FBB uptake in the parietal (standardized $\beta=-0.08$; $p=0.011$; $Q=0.036$), occipital ($\beta=-0.07$; $p=0.018$; $Q=0.036$) and posterior cingulate cortex ($\beta=-0.10$; $p=0.017$; $Q=0.036$) compared to the low STG group ([Figure 1](#), [Table 2](#)). The high STG group was associated with higher FBB uptake in the striatum ($\beta=0.10$, $p=0.001$, $Q=0.008$) relative to the low STG group. However, the STG group was not associated with global FBB uptake ($\beta=-0.06$; $p=0.050$; $Q=0.067$).

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 eight (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 ($p_{\log\text{-rank}}=0.038$, [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 3](#)). 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 S2](#)).

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

During the follow-up period, LID developed in six (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 ($p_{\log\text{-rank}}=0.021$, [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 3](#)). Sensitivity analysis

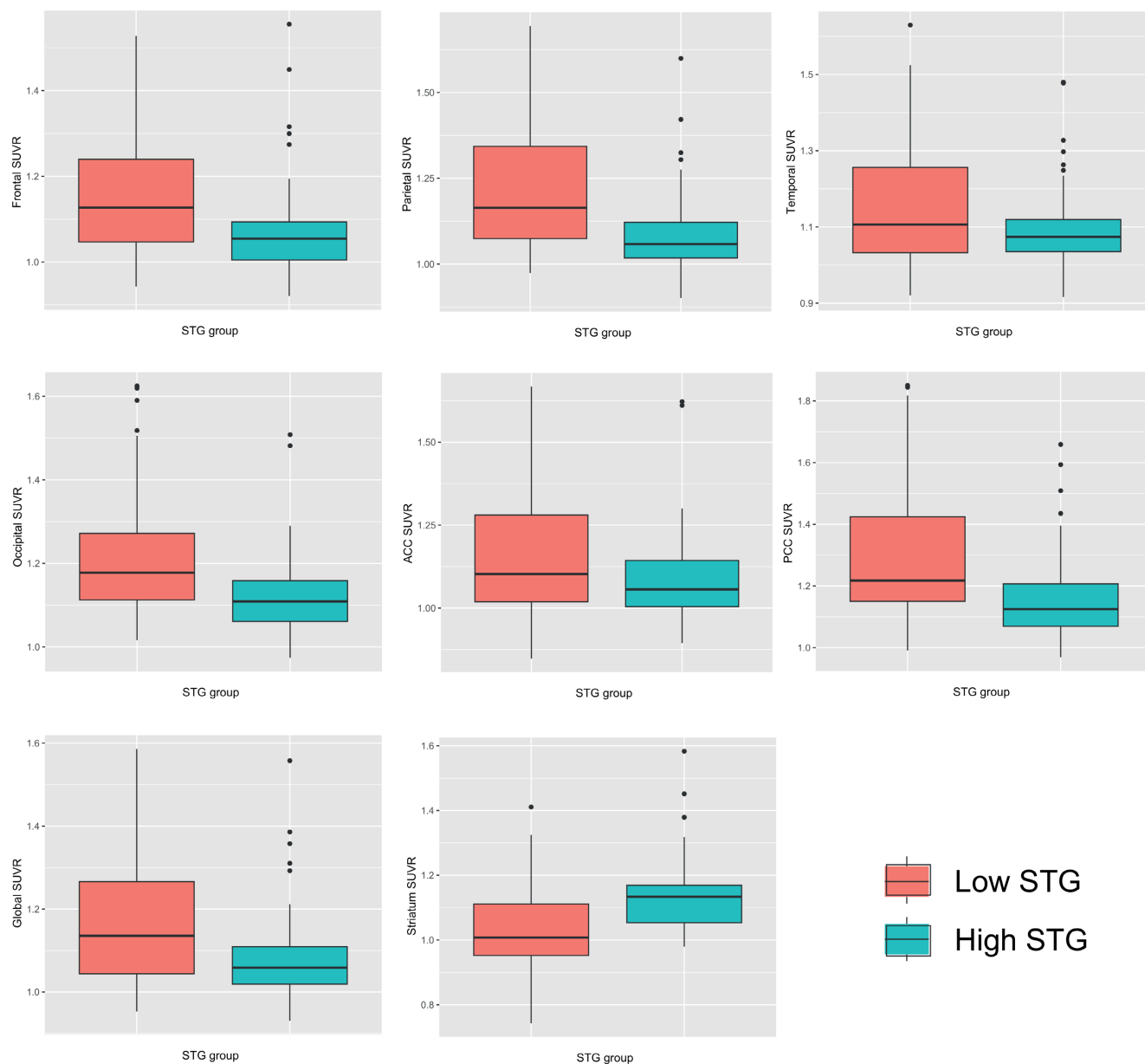


FIGURE 1 Box-and-whisker plots of regional SUVR according to STG group. Patients in the high STG group showed lower regional SUVR in the parietal, occipital and posterior cingulate cortices and higher regional SUVR in the striatum. ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; STG, striatum to global ratio; SUVR, standardized uptake value ratio.

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 S2).

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

During the follow-up period, FoG developed in four (8.3%) and nine (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 ($p_{\log\text{-rank}}=0.241$, 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 3). 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 S2).

Longitudinal assessment of the changes in LEDs between the groups

The STG group $\times$ time interaction term in the linear mixed model was statistically significant ($\beta=1.50$; standard error [SE]=0.33; $p<0.001$; Table 4, Figure 3) after adjusting for potential confounding factors, indicating that the high STG group requires 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 S3). Information on antiparkinsonian medications at the time of the FBB-PET scan is available in Table S4.

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: (i) 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; (ii) patients in the high STG group had a higher risk of developing WO and LID throughout the follow-up period, whilst the risk for FoG was comparable between the two groups; and (iii) 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

TABLE 2 Effect of the high STG group on regional amyloid deposition.

	β (SE)	<i>p</i> 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

Note: 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 reference. Q values are corrected *p* values for multiple comparisons using the false discovery rate method.

Abbreviations: FBB, ^{18}F -florbetaben; SE, standard error; STG, striatum to global ratio; SUVR, standardized uptake value ratio.

TABLE 3 Cox regression analyses of motor complications according to STG group.

	Hazard ratio (95% CI)	<i>p</i> Value
Wearing off		
Age at FBB-PET, years	0.966 (0.924–1.009)	0.121
Sex, female	2.493 (1.039–5.986)	0.041
Disease duration at FBB-PET, months	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, years	1.011 (0.962–1.063)	0.668
Sex, female	3.389 (1.215–9.450)	0.020
Disease duration at FBB-PET, months	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, years	0.926 (0.860–0.998)	0.043
Sex, female	0.095 (0.013–0.720)	0.023
Disease duration at FBB-PET, months	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

Note: 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.

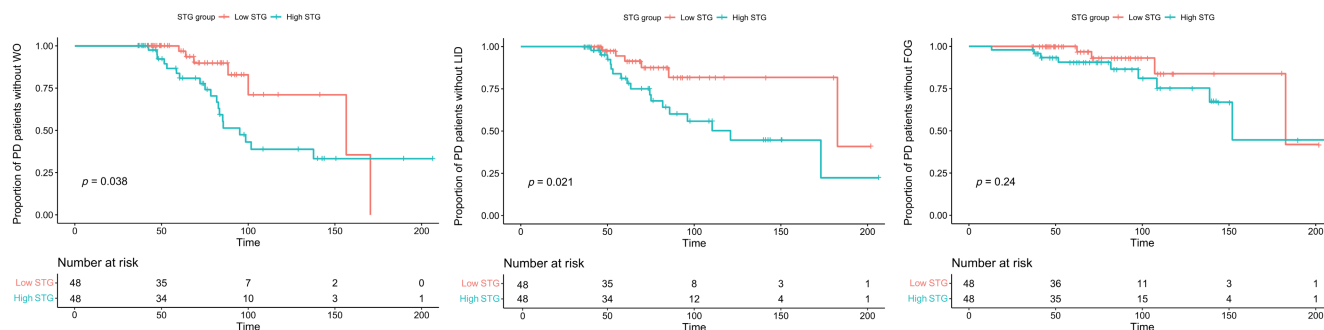


FIGURE 2 Kaplan–Meier survival curve of developing WO, LID and FoG. Curves of Kaplan–Meier estimates of developing WO, LID and FoG after symptom onset in the high STG group (in green) and low STG group (in red). Patients in the high STG group showed a higher risk of WO and LID during the follow-up period.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

TABLE 4 Longitudinal changes in the levodopa equivalent dose according to 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	

Note: 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, ^{18}F -florbetaben positron emission tomography; LED, levodopa equivalent dose; SE, standard error; STG, striatum to global ratio.

patients with AD is thought to begin in the neocortex, spread into the allocortex, and then into the deep grey matter such as the striatum and thalamus, and finally extend into the cerebellum and brainstem [25]. 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 [26]. Moreover, patients with genetic predisposition have earlier and more prominent striatal amyloid deposition than neocortical amyloid deposition [14,27]. 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 rather 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, a previous neuropathological study revealed more severe pathological amyloid burden in the striatum compared to the neocortex in demented PD [12]. In the present study, the relative burden of striatal amyloid over the global amyloid deposition was used, 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 [14,28]. Therefore, the 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 [29]; however, the present study showed that the high STG group showed younger age at FBB-PET scan compared to the low STG group. 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, it was found that the 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 [30–33]. Although WO represents hypokinetic disturbance whilst LID reflects hyperkinetic disturbance, both presynaptic dopaminergic depletion and extra-nigral factors were associated with WO and LID in prior studies [17,34–37]. In this 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 or extra-nigral 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 [38]. 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 [39], 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 [40], and thus a relative striatal amyloid load may not affect the incidence of FoG in this study.

In terms of the 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 partly attributable to the poor response to dopaminergic medications in the high STG group. Alternatively, this finding also suggests that pathological conditions related to

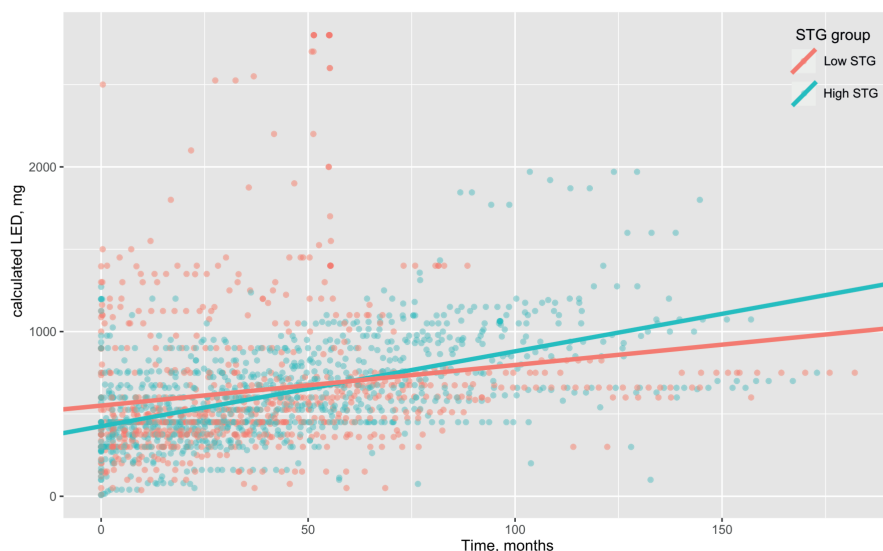


FIGURE 3 Association between STG group and levodopa equivalent dose (LED) over time. A linear mixed model analysis showed a significant difference between the high STG (in green) and low STG (in red) groups (STG group $\times$ time interaction, $p < 0.001$). STG, striatum to global ratio.

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 [41,42], as well as genetic factors [43], would affect the longitudinal prognosis of motor deficits, PD patients with high STG may be prone to have faster increment in the LED required to maintain favourable 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, the STG ratio was adopted to investigate the relative abundance of striatal amyloid in each participant. Second, the patients were divided 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, additional sensitivity analyses were performed controlling for putaminal DAT availability for participants whose DAT imaging was available, revealing similar results to those without controlling putaminal DAT availability. Moreover, the baseline UPDRS-III score and disease duration and LED at FBB-PET scans were comparable between the high and low STG groups. Finally, an analysis to examine the association between region-specific striatal β -amyloid trajectories and each motor complication was not performed due to small sample size. A further clustering analysis would be required to uncover this issue.

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 medication. These findings suggest that relatively high striatal amyloid deposition, which can be

assessed in vivo by PET imaging, may serve as a marker for motor prognosis in patients with PD.

AUTHOR CONTRIBUTIONS

Mincheol Park: conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing. Hyun Joo Kim, Kyoungwon Baik and Han Kyu Na: formal analysis, visualization, validation. Young-gun Lee, So Hoon Yoon, Seong Ho Jeong, Seok Jong Chung, Hae-Won Shin, Chul Hyoung Lyoo and Young H. Sohn: resources, supervision, validation, review. Phil Hyu Lee: conceptualization, methodology, project administration, supervision, writing, review and editing. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Korea Health Technology R&D Project through the Korean Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number HU21C0053) awarded to Phil Hyu Lee.

CONFLICT OF INTEREST STATEMENT

All authors declare no financial or non-financial competing interests.

DATA AVAILABILITY STATEMENT

The de-identified data that support the findings of this study are available from the corresponding author on reasonable request. The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request from the corresponding author.

ORCID

Mincheol Park  <https://orcid.org/0000-0003-2714-7494>

Young-gun Lee  <https://orcid.org/0000-0003-0460-455X>

So Hoon Yoon  <https://orcid.org/0000-0003-3265-3965>

Seong Ho Jeong  <https://orcid.org/0000-0003-4439-4390>
 Seok Jong Chung  <https://orcid.org/0000-0001-6086-3199>
 Hae-Won Shin  <https://orcid.org/0000-0001-6050-7733>
 Chul Hyung Lyoo  <https://orcid.org/0000-0003-2231-672X>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Park M, Kim HJ, Baik K, et al. Association between striatal amyloid deposition and motor prognosis in Parkinson's disease. *Eur J Neurol*. 2024;31:e16364. doi:[10.1111/ene.16364](https://doi.org/10.1111/ene.16364)