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White matter hyperintensities as a predictor of freezing of gait in Parkinson's disease

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ABSTRACT

Introduction: To investigate the effect of white matter hyperintensities (WMH) on long-term motor outcomes in Parkinson's disease (PD).

Methods: We retrospectively reviewed medical records of 268 patients with de novo PD (follow-up > 3 years). According to the Clinical Research Center for Dementia of South Korea (CREDOS) WMH visual rating scale scores, the patients were divided into two groups: a PD group with minimal WMH (PD-WMH-; n = 198) and a PD group with moderate to severe WMH (PD-WMH+; n = 70). We compared longitudinal increases in doses of dopaminergic medications between the two groups using a mixed model. We also assessed the effects of WMH on the development of freezing of gait (FOG).

Results: Patients in the PD-WMH + group were older than those in the PD-WMH- group, and had more severe motor deficits and more severely decreased striatal dopamine transporter availability. The PD-WMH + group required higher doses of dopaminergic medications for symptom control, compared to the PD-WMH- group, over the follow-up period. After adjusting for age, sex, striatal dopamine transporter availability, and levodopa-equivalent dose, the PD-WMH + group showed a higher risk of developing FOG (HR, 3.29; 95% CI, 1.79–6.05; p < 0.001) than the PD-WMH- group.

Conclusion: This study demonstrates that WMH burden negatively affects the longitudinal requirement of dopaminergic medication and the development of FOG. These findings suggest that baseline WMH severity or volume may be a useful prognostic marker of motor outcomes in PD.

1. Introduction

White matter hyperintensities (WMH) are commonly observed in brain imaging studies of healthy elderly individuals [1]. These changes are not merely incidental findings, but have a clinical impact on motor function in older age. Ample evidence has suggested that WMH are related to impairments in gait and balance [2] and incident parkinsonism [3], and the interruption of the frontal subcortical motor circuits may be responsible for this motor disability [4]. Moreover, white matter (WM) integrity appears to be aligned with the nigrostriatal synaptic dopamine function by sharing a common biological mechanism [5]. Accordingly, these findings suggest that comorbid WMH might contribute to the clinical severity in early stages as well as to the progression of Parkinson's disease (PD).

Until now, a number of studies have investigated the association between comorbid WMH and clinical symptoms of PD. Most studies have demonstrated that increased WMH burden is associated with severe motor deficits, especially axial motor impairments [6–11], while some studies failed to show this association [12]. However, most studies have been cross-sectional in nature, and the longitudinal effects of WMH on motor outcomes in PD have thus not yet been evaluated. Therefore, in this study, we investigated whether WMH severity at baseline could determine disease progression regarding motor aspects of parkinsonism in de novo PD. Given that the clinical progression in PD is mainly characterized by worsening motor symptoms [13], we focused on two clinical parameters, namely longitudinal requirement of dopaminergic medications and freezing of gait (FOG), according to the severity of WMH in PD.

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2. Methods

2.1. Subjects

We reviewed the medical records in the Yonsei Parkinson Center database of 394 consecutive patients with de novo PD who visited the movement disorders outpatient clinic at Severance Hospital between April 2009 and June 2014. Of these, 77 patients who were lost to follow-up within 3 years and 31 patients who did not undergo brain MRI scans were excluded from the study. Eighteen patients who showed FOG at the first visit were also excluded (Fig. S1). PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank, and all subjects showed decreased dopamine transporter (DAT) availability in the posterior putamen on ^{18}F-FP-CIT PET scans. Parkinsonian motor symptoms were assessed using the Unified Parkinson's disease Rating Scale Part III (UPDRS-III). Olfactory function was measured with the cross-cultural smell identification test (CCSIT), and depression was evaluated using the Beck Depression Inventory (BDI). The Korean version of the Mini-Mental State Examination (K-MMSE) was used to assess general cognition, and PD medication doses were calculated as levodopa-equivalent doses (LED) [14]. We classified the patients into the tremor-dominant or postural instability/gait difficulty (PIGD) clinical phenotypes based on their UPDRS scores [15]. This study was approved by the Yonsei University Severance Hospital institutional review board, and the need for informed consent was waived because of the retrospective nature of the study.

2.2. Classification of the patients with PD according to WMH

The WMH scores of all 268 patients with de novo PD who were finally enrolled in this study were rated using the Clinical Research Center for Dementia of South Korea (CREDOS) WMH visual rating scale, which correlated well with the automatically measured WMH volume [16]: The modified Fazekas scale was used to describe the extent of periventricular and deep WMH [17]. Then, we divided the patients into two groups according to the CREDOS ischemia classification system: a PD group with minimal WMH (PD-WMH-; n = 198) and a PD group with moderate to severe WMH (PD-WMH+, n = 70; see supplementary methods). Additionally, we also assessed the WMH of each patient using the Scheltens scale in which periventricular and lobar WMH as well as basal ganglia and infratentorial signal hyperintensities are rated separately in semi-quantitative manner [18]. The WMH rating was performed by two neurologists (LYH and YHS) unaware of the clinical information, and a final consensus rating was used for the analysis.

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

We used the same methodology to obtain and analyze the ^{18}F-FP-CIT PET data as previously described (supplementary methods) [19].

2.4. Longitudinal assessment of the changes in LED over time

The patients with PD visited the outpatient clinic with 3-month intervals between visits for at least 3 years, and the doses of these patients' PD medications were adjusted for effective symptom control. We compared the rate of the longitudinal changes in LED between the PD groups with a mixed model. Five fixed effects were included in the model: four were between-subject effects (PD group according to WMH, age at PD onset, sex, and baseline DAT availability in the posterior putamen) and one was a within-subjects effect (time). Since most increases in LED generally occurred within the first 6 months and then the doses of dopaminergic medications were adjusted every 3 months, we treated time as a categorical variable with 6-month intervals (0–36). The effects of PD group on changes in LED over time were tested with a time × PD group interaction term.

2.5. Assessment of the development of freezing of gait during the follow-up

FOG is defined as an unintentional and temporary phenomenon where the feet fail to progress forward, despite an intention to walk [20], and various subtypes are identified as follows: (1) start hesitation at the initiation of walking; (2) freezing on turning; (3) freezing in restricted areas; (4) destination freezing; (5) open-space hesitation in the absence of stimuli likely to result in FOG. We asked patients about the development of FOG at every visit. With respect to FOG, we inspected the patients' gait ("on" status) at the outpatient clinic and specifically asked about the characteristic sensation of the feet becoming "glued to the floor." The time from parkinsonian symptom onset to the occurrence of FOG was assessed with Kaplan-Meier estimates in the 70 patients with moderate to severe WMH and the 198 patients with minimal WMH. A log-rank test was used to compare the Kaplan-Meier plots between the PD groups. To assess the effect of WMH on the development of FOG, the Cox regression model was used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) while adjusting for age at PD onset, sex, DAT availability in the posterior putamen, and LED at the development of FOG or at the last visit to the outpatient clinic.

2.6. Statistical analyses

The baseline demographic characteristics of the PD groups were compared with Student's *t*-tests and Pearson's χ^2 tests. We compared the WMH rated by the Scheltens scale using the Mann-Whitney *U* test. To compare the DAT availability of each striatal sub-region, an analysis of covariance was used while adjusting for age, sex, and PD duration as covariates, and a false discovery rate (FDR)-controlling method was used for multiple-comparison correction [21]. A linear mixed model was used to assess the longitudinal changes in LED. The effects of WMH on the development of FOG were assessed with a log-rank test and the time-dependent Cox regression model. The statistical analyses were performed with SPSS (version 23.0; IBM Corporation, Armonk, NY, USA), and results with a two-tailed p-value < 0.05 were considered statistically significant.

3. Results

3.1. Baseline clinical characteristics of the patients with PD

The patients in the PD-WMH + group (n = 70) were older and had higher UPDRS-III scores than those in the PD-WMH- group (n = 198). The PD-WMH + group showed a greater WMH burden in the periventricular, lobar, basal ganglia, and infratentorial regions than the PD-WMH- group, based on the Scheltens scale [18]. The PD-WMH + group had a higher prevalence of hypertension (p = 0.035) and diabetes mellitus (p = 0.030) and a higher risk of developing a heart attack or stroke over the next 10 years (p < 0.001) than the PD-WMH- group. The tremor-dominant subtype tended to be less prevalent in the PD-WMH + group than in the PD-WMH- group. There were no significant differences in sex, PD duration, CCSIT, BDI, and K-MMSE scores between the groups. The PD-WMH + group exhibited more severely decreased DAT availability in the all striatal sub-regions than the PD-WMH- group (Table 1). Additionally, the PD-WMH + group had a higher risk of development of dementia than the PD-WMH- group (HR, 2.565; 95% CI [1.442, 4.629]; p = 0.002), while adjusting for age at PD onset, sex, years of education, and baseline K-MMSE scores (see supplementary methods, supplementary results, Table S1, and Fig. S3).

3.2. The effect of WMH on the longitudinal changes in LED over time

There was a significant interaction between PD group and time in the mixed model (p = 0.003), indicating that the pattern of longitudinal changes in LED differed between the PD group. The PD-WMH + group required higher doses of dopaminergic medications

Table 1
Baseline demographic characteristics and striatal dopamine transporter availability in patients with PD.

	PD-WMH - (n = 198)	PD-WMH + (n = 70)	*p*-value
Demographic characteristics			
Age (years)	63.42 ± 70.90	70.90 ± 7.91	< 0.001
Female, No. (%)	101 (51.0%)	35 (50.0%)	0.884
Onset of age (years)	61.97 ± 9.68	69.47 ± 7.94	< 0.001
PD duration (years)	17.41 ± 15.17	17.13 ± 16.24	0.896
UPDRS-III	22.06 ± 9.86	26.83 ± 9.91	0.001
CCSIT	6.86 ± 2.34	6.35 ± 2.54	0.143
BDI	12.79 ± 8.88	12.52 ± 8.07	0.826
K-MMSE	27.00 ± 2.94	26.28 ± 2.56	0.077
Scheltens scale [a]			
Periventricular WMH	2.00 (1.00, 3.00)	5.00 (4.00, 6.00)	< 0.001
Lobar WMH	3.00 (1.00, 5.00)	10.50 (8.00, 13.00)	< 0.001
Basal ganglia WMH	0.00 (0.00, 1.00)	1.00 (0.00, 5.00)	< 0.001
Infratentorial WMH	0.00 (0.00, 0.00)	0.00 (0.00, 1.25)	< 0.001
Total WMH	5.00 (3.00, 8.00)	18.00 (14.00, 23.00)	< 0.001
Vascular risk factors			
Hypertension	68 (34.3%)	34 (48.6%)	0.035
Diabetes mellitus	24 (12.1%)	16 (22.9%)	0.030
Dyslipidemia	29 (14.6%)	8 (11.4%)	0.502
Cardiac disease	15 (7.6%)	8 (11.4%)	0.323
Body mass index	23.58 ± 3.03	23.15 ± 3.19	0.316
QRISK3-2018 [b]	15.55 ± 11.66	25.21 ± 13.78	< 0.001
Phenotype			0.033
Tremor dominant	134 (68.0%)	40 (57.1%)	
PIGD	56 (28.4%)	22 (31.4%)	
Intermediate	7 (3.6%)	8 (11.4%)	
DAT availability [c]			
Anterior caudate	2.144 (0.043)	1.921 (0.075)	0.008
Posterior caudate	1.382 (0.034)	1.241 (0.059)	0.049
Anterior putamen	2.204 (0.042)	2.047 (0.072)	0.077
Posterior putamen	1.331 (0.030)	1.196 (0.052)	0.028
More affected side	1.108 (0.027)	1.042 (0.046)	0.231
Less affected side	1.549 (0.036)	1.353 (0.062)	0.008
Ventral putamen	1.450 (0.026)	1.332 (0.046)	0.032
Ventral striatum	2.235 (0.043)	2.034 (0.074)	0.019

Values are expressed as mean ± standard deviation or number (percentage) for the demographic characteristics, median (Q1, Q3) for the Scheltens scale, and estimated mean (standard error) for the striatal DAT availability. Abbreviations: PD, Parkinson's disease; PD-WMH-, PD group with minimal white matter hyperintensities (WMH); PD-WMH+, PD group with moderate to severe WMH; UPDRS-III, the Unified Parkinson's disease Rating Scale Part III; CCSIT, the cross-cultural smell identification test; BDI, the Beck Depression Inventory; K-MMSE, the Korean version of the Mini-Mental State Examination; PIGD, postural instability/gait difficulty; DAT, dopamine transporter.

[a] Journal of the Neurological Sciences 1993; 114:7–12.

[b] We used the QRISK3-2018 scores (https://qrisk.org/three/) to calculate a person's risk of developing a heart attack or stroke over the next 10 years.

[c] To compare the striatal DAT availability, an ANOVA was used while adjusting for age, sex, and PD duration as covariates, and a FDR-controlling method was used for multiple comparisons correction.

than the PD-WMH- group to control parkinsonian symptoms throughout the follow-up period (estimated LED, 474.03 in the PD-WMH + group and 413.13 in the PD-WMH- group at the 1-year follow-up, p = 0.005; 520.03 in the PD-WMH + group and 451.13 in the PD-WMH- group at the 2-year follow-up, p = 0.001; 567.01 in the PD-WMH + group and 503.09 in the PD-WMH- group at the 3-year follow-up, p = 0.003; Table 2 and Fig. S2).

3.3. The effect of WMH on the development of FOG

During the follow-up period, FOG developed in 25 out of the 70 patients in the PD-WMH + group (follow-up duration, 5.03 ± 1.43 years) and in 27 out of the 198 patients in the PD-WMH- group (follow-up duration, 5.86 ± 1.63 years; Fig. 1). The Kaplan-Meier analyses revealed that the risk of developing FOG was higher in the PD-WMH + group than in the PD-WMH- group ($P_{Log\text{-}rank}$ < 0.001). The Cox proportional hazard model revealed that the PD-WMH + group had a higher risk of development of FOG than the PD-WMH- group (HR, 3.292; 95% CI [1.791, 6.048]; p < 0.001; Table 3).

4. Discussion

The present study investigated the effects of baseline WMH on long-term motor outcomes in patients with de novo PD. The major findings were as follows: (1) The patients with PD with moderate to severe WMH were older and had higher UPDRS-III scores as well as more severely decreased striatal DAT availability than the patients with minimal WMH at baseline. (2) The patients with PD with moderate to severe WMH required higher doses of dopaminergic medications for symptom control than those with minimal WMH over the follow-up period. (3) The PD group with moderate to severe WMH had a higher risk for developing FOG than the PD group with minimal WMH, after adjustments for the confounding effects of age, sex, and DAT availability in the posterior putamen, and LED. These findings suggest that baseline WMH severity or volume can act as a prognostic marker for future motor disability in patients with de novo PD.

There is increasing evidence of the association between WMH and parkinsonian signs, especially gait and balance disturbances in older people [2]. Although the mechanisms linking WMH and motor disability are not fully understood, it is widely accepted that WM alterations may disconnect the primary motor cortex and supplementary motor area from the basal ganglia and cerebellum [22], which then leads to parkinsonism. The WMH burden in the periventricular frontal regions may be of particular importance, given that major tracts linked to high-order motor control, such as the ascending thalamocortical and descending corticospinal fibers, corpus callosum, and brainstem long tract pathways, may be easily disrupted [10,23]. Furthermore, WMH appear to exert their action outside the visible lesions by either perilesional or remote effects [24], and their clinical impact on motor disability may be greater than predicted by MRI findings.

Therefore, comorbid WMH could, plausibly, affect the clinical severity or features in patients with PD [25]. WMH are commonly found in about 30–50% of patients with PD [6], and several previous studies have reported the negative influence of WMH on motor symptoms in PD [6–11]: WMH have generally been associated with severe motor deficits [6,8,9], axial motor impairments [7,9,10] or PIGD subtype [25], and poor levodopa response [7,11], even though some studies failed to show this association [12]. The mechanisms by which WMH contribute to motor symptoms of PD may be either additive or synergistic to the neurodegenerative process [26]. Besides the interruption of the frontal subcortical motor circuits by WM lesions (additive effect), vascular pathology does damage to the capillary network in multiple brain regions, particularly in the substantia nigra, frontal cortex, and brainstem nuclei in PD. This damage of the capillary network can make the brain tissue more vulnerable to the neurodegenerative process (synergistic effect), via increased oxidative stress, inflammatory responses, and breakdowns of the blood-brain barrier [26]. Indeed, Rodriguez-Perez et al. [5] showed that chronic cerebral hypoperfusion induced a significant loss of nigral dopaminergic neurons in a rat model. In addition, other processes other than vascular pathology may contribute to WMH, including low-grade inflammation, Wallerian degeneration, and axonal transport disruption [9]. In this regard, comorbid WMH may indicate a higher pathological burden, which is either degenerative or non-degenerative, in patients with PD. In accordance with previous literature, patients in the PD-WMH + group in the current study had higher UPDRS-III scores and more severely decreased striatal DAT availability than those in the PD-WMH- group. In addition, there was a significant difference in the proportions of motor phenotypes between the PD

Table 2
Longitudinal changes in levodopa-equivalent dose.

	PD-WMH- (n = 198)	PD-WMH+ (n = 70)	Overall p-value[a]	p-value[b]
Month 6	385.195 (10.519)	437.091 (18.741)		0.016
Month 12	413.131 (10.493)	474.026 (18.741)	Group: < 0.001	0.005
Month 18	432.732 (10.544)	499.510 (18.741)	Time: < 0.001	0.002
Month 24	451.134 (10.491)	520.034 (18.741)	Group × Time: 0.003	0.001
Month 30	474.926 (10.519)	540.841 (18.741)		0.002
Month 36	503.087 (10.490)	567.010 (18.741)		0.003

Values are expressed as estimated mean (standard error) for levodopa-equivalent dose. Abbreviations: PD-WMH-, PD group with minimal white matter hyperintensities; PD-WMH+, PD group with moderate to severe white matter hyperintensities.
[a] P-values calculated by a linear mixed model analysis.
[b] Group comparison at each time point.

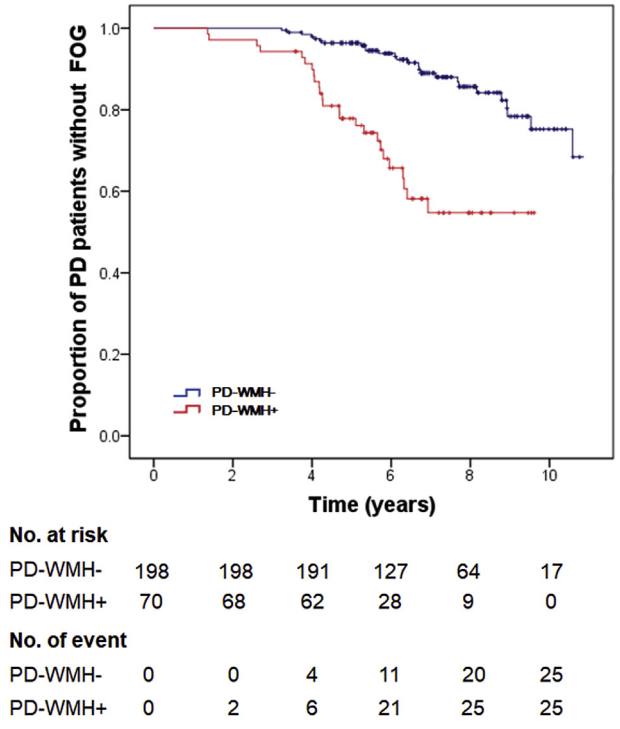

Fig. 1. Curves of Kaplan-Meier estimates of the onset of freezing of gait (FOG) after parkinsonian symptom onset in patients with moderate to severe WMH (n = 70) and matched patients with minimal WMH (n = 198). The PD-WMH + group had a higher risk of development of FOG than the PD-WMH- group ($P_{Log\text{-}rank}$ < 0.001). The crosses in the graphs indicate censored data. Abbreviations: PD-WMH-, PD group with minimal white matter hyperintensities; PD-WMH+, PD group with moderate to severe white matter hyperintensities.

Table 3
Cox regression analysis for the development of freezing of gait according to white matter hyperintensities.

Factors	Hazard ratio (95% CI)	p-value
Group (PD-WMH + vs. PD-WMH-)	3.292 (1.791, 6.048)	< 0.001
Age at PD onset	1.028 (0.994, 1.063)	0.099
Sex (Female vs. Male)	1.232 (0.704, 2.154)	0.465
DAT availability in posterior putamen	0.711 (0.356, 1.421)	0.334
LED	1.000 (0.999, 1.001)	0.807

Abbreviations: PD, Parkinson's disease; PD-WMH+, PD group with moderate to severe white matter hyperintensities; PD-WMH-, PD group with minimal white matter hyperintensities; DAT, dopamine transporter; LED, levodopa-equivalent; CI, confidence interval.

groups. Moreover, the risk for the conversion to dementia was higher in the PD-WMH + group than that in the PD-WMH- group, suggesting that the pathological burden may be greater in the PD-WMH + group.

This is the first report to explore the longitudinal effect of WMH burden on the progression of PD over the follow-up period. In fact, some previous studies have reported the association between WMH and disease progression in PD [6,7,10]. However, these studies, due to their cross-sectional nature, estimated disease progression as the ratio between the Hoehn and Yahr stage or UPDRS-III scores and disease duration; this method is however unable to reflect the true slope of the motor decline in early PD [10]. Song et al. [27] conducted a 2-year follow-up study to reveal that silent cerebral ischemic lesions did not have significant effects on the progression of PD. However, even though this was a longitudinal study, it had limitations because only a small sample of patients with PD with mild WMH were enrolled.

In the present study, we assessed the following two clinical parameters as the disease progression index: (1) the longitudinal requirement of dopaminergic medications in response to the need for symptom control and (2) the risk for the development of FOG. First, we assessed the rate of clinical progression according to the longitudinal changes in doses of PD medications. Indeed, changes in LED can be clinically meaningful measures in early stages of PD. In this study, the PD-WMH + group required higher doses of dopaminergic medications than the PD-WMH- group throughout the follow-up period, even after adjusting for the DAT availability in the posterior putamen. The pattern of longitudinal changes in LED significantly differed between the groups (i.e., a significant interaction between PD group and time in the mixed model), and thus baseline WMH appears to determine the rate of disease progression. Our finding also suggests that the deleterious effect of WMH on motor severity in PD would be maintained over the follow-up period. In addition, this finding might be partially attributable to poor responses to levodopa in the PD-WMH + group [7,11]. Second, FOG rarely occurs in early PD but is one of the key features of advanced PD. The underlying pathophysiology leading to FOG is complex and remains largely unknown. Several studies have suggested that diffuse WM damage involving major cortico-cortical, motor-related cortico-fugal, and several striato-frontal tracts in addition to the cerebellar and pedunculopontine nuclei is implicated in FOG [28,29]. However, the rate at which these axial motor impairments develop is not easily predicted due to inter-individual variability. Our finding that the PD-WMH + group had a higher risk for developing these axial motor impairments suggests that baseline WMH can be used as a clinically relevant predictor of FOG in patients with PD. Further studies using imaging techniques with higher sensitivity, such as diffusion tensor imaging (DTI) or functional MRI, are needed to confirm our longitudinal findings.

Our study has some limitations. First, the PD groups were classified based on the CREDOS ischemia classification system [16]. This WMH visual rating scale might be less accurate than other more segmented scales (e.g., the Scheltens scale [18]). However, this scale correlates well with the automatically measured WMH volume [16], and we also

found significant differences in the Scheltens scale scores between the groups. In addition, the lack of DTI data is another limitation, given that widespread microstructural WM alterations may occur before WMH are visually apparent on brain MRI [25]. Second, periventricular and deep WMH may have different pathogenic mechanisms [30] and different effects on motor disability. Indeed, some studies found that periventricular WMH were more closely linked to parkinsonism than deep WMH [6], while others did not [7]. However, this issue does not matter for the current study, since minimal periventricular WMH (P1) were observed in most patients (74.3%) in the PD-WMH- group, but only in a small sample (17.1%) in the PD-WMH + group. Third, the occurrence of FOG was not evaluated with objective gait measures, although we tried our best to avoid missing newly developed cases of FOG. Fourth, individual variability in the intensity of vascular risk factor treatments, which are difficult to assess in a retrospective study, might act as a confounding factor. Finally, it is unclear in which extent the WMH in contrast to the neurodegenerative process (i.e., PD pathology) influence the clinical parameters, although we included the DAT availability in the posterior putamen as covariates in the statistical models to adjust for the impact of underlying disease as much as possible.

In conclusion, the present study demonstrates that comorbid WMH are associated with long-term motor disability and development of FOG in patients with PD. These findings suggest that baseline WMH severity or volume can be used as a prognostic marker for motor outcomes in PD.

Relevant conflicts of interest/financial disclosures

None declared.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.07.019.

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