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Predictors of freezing of gait in early Parkinson's disease: clinical, dopamine transporter imaging and CSF markers

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ABSTRACT

Predictors of freezing of gait in early Parkinson's disease: clinical, dopamine transporter imaging and CSF markers

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Objective The aim of this study was to determine whether dopamine transporter (DAT) imaging and cerebrospinal fluid (CSF) parameters can be used as a predictor of freezing of gait (FOG) in patients with early Parkinson's disease (PD). In addition, we further investigated the predictive value of clinical, DAT imaging and CSF markers for the development of FOG both separately and in combination.

Methods This cohort study using the Parkinson's Progression Markers Initiative data included a total of 393 early PD patients without FOG. Demographic and clinical data, DAT imaging results, and CSF marker levels including β-amyloid 1-42 ($A\beta_{42}$), α-synuclein, total tau, phosphorylated tau_{181}, and the calculated ratio of $A\beta_{42}$ to total tau were collected at baseline. The FOG data up to 4 years of follow-up were included. The development of FOG was defined to be present if the score was 1 or greater either for the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) item 2.13 or item 3.11 at any point during the follow-up period. Cox regression models were conducted to identify the factors predictive of FOG. Based on these results, we constructed a predictive model for the development of FOG.

Results During a median follow-up of 4.0 years (mean 3.0 years), 136 patients developed FOG, and its cumulative incidence was 17, 21, 28, and 37% at 1-, 2-, 3- and 4-year follow-up, respectively. Among DAT imaging and CSF markers, caudate DAT uptake (hazard ratio [HR] 0.581; 95% confidence interval [CI] 0.408−0.827; p=0.003) and CSF $A\beta_{42}$ (HR 0.997; 95% CI 0.996−0.999; p=0.009) were predictive of FOG. Postural instability gait difficulty (PIGD) score (HR 1.494; 95% CI 1.282−1.741; p<0.001) and, to a lesser extent, male sex (HR 1.512; 95% CI 1.007−2.271; p=0.046), MDS-UPDRS motor score (HR 1.022; 95% CI 1.000−1.045; p=0.046), and Montreal Cognitive Assessment score (HR 0.927; 95% CI 0.860−0.995; p=0.035) were also related to the development of FOG. The combined model integrating the PIGD score, caudate DAT uptake, and CSF $A\beta_{42}$ achieved a better prediction accuracy (area under the curve 0.755; 95% CI 0.700−0.810)

than any factor alone.

Conclusions This study found striatal DAT uptake and CSF $A\beta_{42}$ as predictors of FOG in patients with early PD. Furthermore, FOG development within 4 years after PD diagnosis can be predicted with acceptable accuracy using our risk model.

Keywords: Parkinson's disease; freezing of gait; dopamine transporter; CSF; amyloid; predictor

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Introduction

Freezing of gait (FOG) is defined as a transient and unpredictable break in walking, mainly occurring during gait initiation or turning.[1,2] Although FOG is common in advanced Parkinson's disease (PD) in which the frequency of such symptom is more than 90% in Hoehn and Yahr stage 4, some patients may experience it earlier.[3-5] A previous study has shown that FOG developed in about 25% of patients with early PD over 2 years of follow-up.[6] FOG results in an elevated risk for falls and injuries, functional dependency, and impaired quality of life.[4,7] Accordingly, identification of PD patients who are at risk of developing FOG can provide important prognostic information to patients and their caregivers.

There are several potential mechanisms associated with FOG in PD. Previous studies have revealed that extra-nigral pathologies such as cholinergic deficits and cortical β-amyloid accumulation lead to the development of FOG.[8,9] Striatal dopaminergic denervation is also suggested as a pathomechanism underlying FOG by its improvement via the administration of levodopa.[3,10] Moreover, several neuroimaging studies have shown a relationship between striatal dopamine transporter (DAT) activity and FOG in PD patients.[9,11-13]

Various clinical variables including male sex,[14] longer disease duration,[4,6,14-16] increased motor severity,[4,6,14] severe postural instability gait difficulty (PIGD),[4,6,16-18] impaired cognitive function,[18,19] and anxiety[20] have been regarded as predictors of FOG in PD patients. However, it remains unclear whether DAT imaging and cerebrospinal fluid (CSF) markers can be used as a predictor of FOG. Previous

observations regarding the association between DAT imaging and FOG were limited by the small number of patients and cross-sectional correlation.[9,11,12] Moreover, CSF markers have not been investigated as a means of predicting FOG, although previous studies have shown that CSF β-amyloid 1-42 ($A\beta_{42}$) is associated with PIGD features.[21-23]

Therefore, This study aimed to investigate whether DAT imaging and CSF parameters are related to the development of FOG in early PD patients. Additionally, we further assessed the predictive value of clinical, DAT imaging and CSF markers for the development of FOG both individually and in combination.

Materials and Methods

Patients

The data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database, which were downloaded on June 2017. The PPMI study is an international, cohort study to identify biomarkers associated with PD progression. Early PD patients were recruited from 33 sites in the United States, Europe, Australia, and Israel. The methodology and details of the study assessments are available on the PPMI website (http://ppmi-info.org).

At enrollment, PD patients were required to be aged 30 years or more at diagnosis; have an asymmetric resting tremor or asymmetric bradykinesia, or at least two of the following: resting tremor, bradykinesia, and rigidity; be diagnosed within 2 years; have Hoehn and Yahr stage of less than III; be untreated for PD; and have a DAT deficit on single photon emission computed tomography (SPECT) scans. After enrollment, patients were followed up at 3-month intervals in the first year and 6-month intervals in the subsequent years. For this study, data up to 4 years of follow-up were included.

Approval was obtained from an ethical standards committee on human experimentation for all experiments with human participants before the initiation of the study. Written informed consent was received from all participants. The study was registered in clinicaltrials.gov as NCT01141023.

Assessment of FOG

FOG was assessed with the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) item 2.13 (freezing) and item 3.11 (freezing of gait). The FOG development was defined to be present if the score was 1 or greater either for MDS-UPDRS item 2.13 or item 3.11 at any point during the follow-up period.

DAT SPECT imaging

All patients received 111 to 185 MBq (3 to 5mCi) of ^{123}I-Ioflupane intravenously, and the acquisition was conduced between 3.5 and 4.5 hours after the injection. Raw projection data were obtained with a 128 x 128 matrix in a step and shoot mode and then were imported to the Hermes software (Medical Solutions, Stockholm, Sweden) for iterative reconstruction. The reconstructed files were transferred to Pmod (PMOD Technologies, Zurich, Switzerland) for subsequent processing. Regions of interest were placed on the ipsilateral and contralateral caudate, the ipsilateral and contralateral putamen, and the occipital cortex (reference tissue). The striatal binding ratio for each of the 4 striatal regions was measured as follows: [(target region/reference region) - 1]. For this study, we used the mean caudate binding ratio (average of ipsilateral and contralateral caudate binding ratios) and mean putamen binding ratio (average of ipsilateral and contralateral putamen binding ratios).

CSF markers

CSF samples were shipped from the PPMI Biorepository Core laboratories to the University of Pennsylvania and to Covance for analyses. CSF $A\beta_{42}$, total tau (t-tau) and phosphorylated tau_{181}

(p-tau) were analyzed with the xMAP-Luminex platform with INNOBIA AlzBio3 immunoassay kit-based reagents (Fujirebio-Innogenetics, Ghent, Belgium), and CSF α-synuclein was analyzed with commercially available enzyme-linked immunosorbent assay kit (Covance, Dedham, MA). We used the CSF data for $A\beta_{42}$, α-synuclein, t-tau, p-tau, and the calculated ratio of $A\beta_{42}$ to t-tau in this study.

Clinical variables

Motor symptoms were assessed with the MDS-UPDRS part 3. Tremor and PIGD scores were also calculated using the both MDS-UPDRS parts 2 and 3. The tremor score was the sum of the following eleven items: 2.10 (tremor), 3.15a (postural tremor RUE), 3.15b (postural tremor LUE), 3.16a (kinetic tremor RUE), 3.16b (kinetic tremor LUE), 3.17a (rest tremor RUE), 3.17b (rest tremor LUE), 3.17c (rest tremor RLE), 3.17d (rest tremor LLE), 3.17e (rest tremor lip/jaw), and 3.18 (rest consistency). The PIGD score was the sum of the following three items: 2.12 (walking and balance), 3.10 (gait), and 3.12 (postural stability). Non-motor symptoms were measured with the University of Pennsylvania Smell Identification Test to assess olfactory function, the REM sleep behavior (RBD) Screening Questionnaire to assess RBD symptoms, the Epworth Sleepiness Scale to assess excessive daytime sleepiness, the Montreal Cognitive Assessment (MoCA) to assess overall cognitive function, the 15-item Geriatric Depression Scale to assess depression, the State-Trait Anxiety Inventory to assess anxiety, and the Scale for Outcomes in Parkinson's disease-Autonomic to assess autonomic function.

Statistical analysis

Baseline characteristics were compared with the chi-square test or the Student's t test, as appropriate. The Kaplan-Meier method was used to estimate the cumulative incidence of FOG. Cox proportional-hazards regression analyses were performed to identify the predictors of FOG. All baseline variables with p value less than 0.1 in the univariable Cox models were inserted into a subsequent multivariable Cox model with a backward elimination procedure (p value removal=0.1). If there was a strong correlation between variables (r>0.5), the variable with the lower p value was entered as an independent variable. For the predictive model combing clinical, DAT imaging, and CSF markers, only independent variables with p<0.01 in the multivariable Cox model were included to restrict the number of predictors for usability and to avoid overfitting of the model.[24] A bootstrap resampling procedure with 1000 repetitions was applied to the final risk model. Based on these results, the risk score was obtained in the following manner: risk score = $(X_1 \times B_1) + (X_2 \times B_2) + (X_3 \times B_3),\cdots, + (X_p \times B_p)$, where X_1, X_2, $X_3,\cdots$, X_p are baseline predictors and B_1, B_2, $B_3,\cdots,B_p$ are the regression coefficients of the baseline predictors 1 to p, respectively.[25] The predictive performance of the models was investigated with the area under the curve (AUC) of the time-dependent receiver operating characteristic (ROC) curves. We tested calibration with the chi-square statistic for goodness of fit. All statistical tests were two-tailed and differences were considered significant at level of <0.05. Calculations were performed with SPSS 18.0 (SPSS Inc., Chicago, IL) and R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 423 PD patients were enrolled in the PPMI study between 2010 and 2013. Of these, 23 patients had FOG at baseline visit, and 7 had no follow-up data. Finally, 393 patients were included in this study. During a median follow-up of 4.0 years (mean 3.0 years), 136 patients developed FOG, and its cumulative incidence was 17, 21, 28, and 37% at the 1-, 2-, 3- and 4-year follow-up, respectively (Figure 1). The baseline characteristics of the patients are presented in Table 1. PD patients with the development of FOG had a more reduced DAT uptake on both caudate and putamen and lower levels of CSF $A\beta_{42}$, t-tau and p-tau compared to those without the development FOG.

DAT imaging and CSF markers as a predictor of FOG

The results of the Cox regression analyses are shown in Table 2. Although both the caudate and putamen DAT activities were significantly correlated with FOG in the univariable Cox analyses, only the caudate DAT uptake with the lower p value was inserted as an independent variable for further analysis considering the multicollinearity between the two variables (r=0.731). All CSF markers except for the ratio of $A\beta_{42}$ to t-tau were entered in a multivariable Cox model. In the multivariable Cox analysis, caudate DAT uptake (hazard ratio [HR] 0.581; 95% confidence interval [CI] 0.408－0.827; p=0.003) and CSF $A\beta_{42}$ (HR 0.997; 95% CI 0.996－0.999; p=0.009) were significantly predictive of FOG. Additionally, male sex

(HR 1.512; 95% CI 1.007−2.271; p=0.046), MDS-UPDRS motor score (HR 1.022; 95% CI 1.000−1.045; p=0.046), PIGD score (HR 1.494; 95% CI 1.282−1.741; p<0.001), and MoCA score (HR 0.927; 95% CI 0.860−0.995; p=0.035) were also associated with the development of FOG.

Predictive value of clinical, DAT imaging, and CSF markers

We further investigated the predictive value of clinical, DAT imaging and CSF markers with a p<0.01 in the multivariable Cox model. Thus, three variables including the PIGD score, caudate DAT uptake, and CSF $A\beta_{42}$ were considered for the final risk model. The bootstrapped Cox regression analysis of the model showed that they all were significantly related to the FOG development (Table 3). Based on these results, the risk score was calculated as follows: 0.438 × PIGD score − 0.622 × mean caudate DAT uptake (striatal binding ratio) − 0.003 × CSF $A\beta_{42}$ level (pg/ml).

Time-dependent ROC curve analyses at the 4-year follow-up showed that the PIGD score had a higher accuracy (AUC 0.684; 95% CI 0.628−0.740) in the prediction of FOG development compared to CSF $A\beta_{42}$ (AUC 0.584; 95% CI 0.518−0.649; p=0.007, Figure 2A) but not compared to caudate DAT uptake (AUC 0.662; 95% CI 0.600−0.725; p=0.624, Figure 2B). There was no difference in the AUC between the CSF $A\beta_{42}$ and caudate DAT uptake (p=0.064, Figure 2C). Combining three parameters using the risk score significantly increased the prediction accuracy (AUC 0.755; 95% CI 0.700−0.810) compared to the PIGD score (p=0.007), caudate DAT uptake (p=0.001), and CSF $A\beta_{42}$ (p<0.001, Figure 2D). This combined model produced

an acceptable goodness of fit (chi-square statistic = 63.648, 3 degrees of freedom; $p<0.001$).

Discussion

This study assessed DAT imaging and CSF parameters as a predictor of FOG in 393 patients with early PD. Over a median follow-up of 4.0 years, we found significant associations of FOG development with reduced striatal DAT uptake and low CSF $A\beta_{42}$ levels at baseline. Moreover, FOG was linked to a number of clinical factors including the PIGD score and, to a lesser extent, male sex, MDS-UPDRS motor score, and MoCA score. Importantly, the risk model combining the PIGD score, caudate DAT activity, and CSF $A\beta_{42}$ achieved a better prediction accuracy than any factor alone.

The frequency of FOG in early PD patients has been reported by several longitudinal studies. The DATATOP clinical trial with 2 years of follow-up showed that FOG developed newly in 193 (26%) of 743 early PD patients without FOG at baseline visit,[6] which is roughly consistent with our result. These findings indicate that quite a number of PD patients can develop FOG even early in the disease course, which is supported by Perez-Lloret et al.[4] who reported that FOG occurred in 10 and 20% of PD patients with the Hoehn and Yahr stage 1 and 1.5, respectively. Conversely, the ELLDOPA clinical trial showed that only 33 (9%) of 361 early PD patients developed FOG over 42 weeks of follow-up.[26] However, unlike the PPMI study, most of the patients in that study received a dopaminergic drug immediately after enrollment, and this could influence the outcome of FOG. In fact, the frequency of FOG in the placebo group of the ELLDOPA study (13/90, 14%) is very similar to our result.

Although striatal dopaminergic denervation is thought to be one of

the presumed causes of FOG, their association has been difficult to demonstrate. There is evidence that the severity of parkinsonian motor symptom as an indirect marker of striatal dopaminergic deficits is related to FOG development.[6] However, motor severity does not accurately reflect the status of the presynaptic dopamine denervation.[27] Although previous functional imaging studies found that FOG was partially attributed to a deficit in the nigrostriatal system,[9, 11, 12] these observations are limited by cross-sectional study design. To the best of our knowledge, this is the first longitudinal study to demonstrate a direct association between the initial presynaptic striatal dopamine loss and the future development of FOG in PD.[28]

This study provides evidence that decreased CSF levels of $A\beta_{42}$ contribute to FOG development in PD patients. CSF $A\beta_{42}$ is a marker of Aβ pathology which is inversely correlated with Aβ plaque formation in the brain.[29] Thus, our results indicate that amyloid deposition in the brain may be one of the contributors to the early development of FOG. The role of Aβ pathology on the occurrence of FOG remains unclear, but several hypotheses may be possible to explain its mechanism.[30] One hypothesis is that the Aβ plaque affects the neural circuitry associated with FOG by influencing on synaptic function directly.[23] Alternatively, one could speculate that amyloid interacts with other proteins such as α-synuclein or tau that catalyze protein misfolding,[31] leading to a rapid progression of FOG. On the other hand, Aβ pathology may have an indirect effect on FOG development via cognitive decline that is closely related to FOG.

One of the main objectives of the current study was to assess the value of a variety of baseline parameters in predicting FOG. Unfortunately, the PIGD score, caudate DAT uptake, and CSF $A\beta_{42}$

had a prediction accuracy with an AUC of less than 0.7. However, the combination of these markers enhanced the prediction accuracy to an AUC of 0.755, indicating that this combined model is more useful to identify people at risk of FOG in early PD. We believe that our risk model will not only provide prognostic information to patients and their caregivers, but also enable the stratification of patients in future clinical trials regarding FOG prevention.

The current study has several limitations. First, the PPMI data could not measure the extent of amyloid pathology contributing to FOG. Further amyloid imaging studies will help to provide a more accurate etiology of FOG. Second, this study included only data up to 4 years of follow-up, which might limit the prediction accuracy of FOG when evaluated over longer periods. Third, since there is a controversy as to which test best identifies the occurrence of FOG, the FOG data in this study might be misestimated. However, we presented the FOG data by combining both subjective (MDS-UPDRS item 2.13) and objective (MDS-UPDRS item 3.11) assessments, and thus, this misestimation is less likely to be significant. Last, FOG typically becomes dopa-resistant as the disease progresses but can be treated with dopaminergic medications particularly in the early stage of PD.[3,32] Therefore, FOG may be underestimated after the initiation of dopaminergic drugs. However, we used all FOG data in the *off*- and *on*-medication states in patients who began treatment for PD. Accordingly, this limitation could only have minor effects on our results.

Conclusion

In summary, we found striatal DAT uptake and CSF $A\beta_{42}$ as predictors for FOG development in early PD patients. Additionally, although our results should be confirmed by further studies, we showed that FOG development within 4 years after PD diagnosis can be predicted with acceptable accuracy using a model combining three independent markers that include the PIGD score, caudate DAT activity and CSF $A\beta_{42}$.

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Tables and Figures

Table 1. Baseline characteristics

Variables	Total patients (n=393)	Patients with FOG development (n=136)	Patients without FOG development (n=257)	*p* value
Clinical markers				
Male sex	259 (66%)	100 (74%)	159 (62%)	0.020
Disease duration, years	1.9 (2.0)	1.8 (1.4)	2.0 (2.2)	0.309
Age at onset, years	60.0 (9.9)	61.7 (9.9)	59.2 (9.8)	0.015
MDS-UPDRS motor score	20.6 (8.7)	22.8 (9.4)	19.4 (8.2)	<0.001
Tremor score	5.4 (3.5)	5.3 (3.5)	5.5 (3.5)	0.752
PIGD score	1.0 (1.0)	1.4 (1.1)	0.8 (0.9)	<0.001
MoCA score	27.1 (2.3)	26.5 (2.5)	27.4 (2.2)	0.001
UPSIT score	22.3 (8.2)	21.0 (8.8)	22.9 (7.9)	0.031
RBDSQ score	4.2 (2.6)	4.5 (2.7)	4.0 (2.5)	0.043
ESS score	5.7 (3.4)	6.3 (3.3)	5.3 (3.4)	0.009
GDS score	2.2 (2.3)	2.6 (2.4)	2.0 (2.3)	0.029
STAI score	64.4 (17.9)	66.2 (18.1)	63.4 (17.8)	0.132
SCOPA-AUT score	9.2 (5.9)	10.4 (6.4)	8.5 (5.6)	0.004
DAT imaging (striatal binding ratio)				
Mean caudate uptake	2.0 (0.5)	1.9 (0.6)	2.1 (0.5)	<0.001
Mean putamen uptake	0.8 (0.3)	0.8 (0.3)	0.9 (0.3)	0.002
CSF markers (pg/ml)				
$A\beta_{42}$	372.3 (101.2)	352.9 (96.9)	382.6 (102.1)	0.006
α-synuclein	1848.2 (786.3)	1751 (724.9)	1899.6 (813.5)	0.079
Total tau	44.8 (18.2)	42.3 (17.4)	46.2 (18.4)	0.044
Phosphorylated tau	15.9 (10.2)	14.2 (7.9)	16.7 (11.2)	0.022
$A\beta_{42}$:tau ratio	9.2 (3.1)	9.3 (3.2)	9.2 (3.1)	0.910

Data are n (%) and the mean (standard deviation).

Abbreviations: $A\beta_{42}$=β-amyloid 1-42; CSF=cerebrospinal fluid; DAT=dopamine transporter; ESS=Epworth Sleepiness Scale; FOG=freezing of gait; GDS=Geriatric Depression Scale; MDS-UPDRS=Movement Disorders Society Unified Parkinson's Disease Rating Scale; MoCA=Montreal cognitive assessment; PIGD=postural instability gait difficulty; RBDSQ=REM Sleep Behavior Disorder Screening Questionnaire; STAI=State-Trait Anxiety Inventory; SCOPA-AUT=Scale for Outcomes in Parkinson's disease-Autonomic; UPSIT=University of Pennsylvania Smell Identification Test.

Table 2. Results of the Cox regression analyses for predictors of freezing of gait

	Univariable analysis		Multivariable analysis	
Variables	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Clinical markers				
Male sex	1.560 (1.066−2.284)	0.022	1.512 (1.007−2.271)	0.046
Disease duration, years	0.941 (0.844−1.049)	0.272		
Age at onset, years	1.025 (1.007−1.043)	0.006	−	−
MDS-UPDRS motor score	1.042 (1.023−1.061)	<0.001	1.022 (1.000−1.045)	0.046
Tremor score	0.995 (0.947−1.046)	0.858		
PIGD score	1.539 (1.347−1.758)	<0.001	1.494 (1.282−1.741)	<0.001
MoCA score	0.899 (0.843−0.957)	0.001	0.927 (0.860−0.995)	0.035
UPSIT score	0.975 (0.955−0.996)	0.019	−	−
RBDSQ score	1.078 (1.014−1.147)	0.016	−	−
ESS score	1.074 (1.026−1.124)	0.002	−	−
GDS score	1.082 (1.016−1.153)	0.015	−	−
STAI score	1.007 (0.998−1.017)	0.115		
SCOPA-AUT score	1.042 (1.017−1.068)	0.001	−	−
DAT imaging				
Mean caudate uptake	0.478 (0.342−0.667)	<0.001	0.581 (0.408−0.827)	0.003
Mean putamen uptake	0.301 (0.149−0.610)	0.001	−	−
CSF markers				
$A\beta_{42}$	0.997 (0.995−0.999)	0.003	0.997 (0.996−0.999)	0.009
α-synuclein	1.000 (1.000−1.000)	0.088	−	−
Total tau	0.991 (0.980−1.001)	0.078	−	−
Phosphorylated tau	0.977 (0.957−0.998)	0.033	−	−
$A\beta_{42}$:tau ratio	0.993 (0.940−1.049)	0.790		

Abbreviations: $A\beta_{42}$=β-amyloid 1-42; CI=confidence interval; CSF=cerebrospinal fluid; DAT=dopamine transporter; ESS=Epworth Sleepiness Scale; GDS=Geriatric Depression Scale; HR=hazard ratio; MDS-UPDRS=Movement Disorders Society Unified Parkinson's Disease Rating Scale; MoCA=Montreal cognitive assessment; PIGD=postural instability gait difficulty; RBDSQ=REM Sleep Behavior Disorder Screening Questionnaire; STAI=State-Trait Anxiety Inventory; SCOPA-AUT=Scale for Outcomes in Parkinson's disease-Autonomic; UPSIT=University of Pennsylvania Smell Identification Test.

Table 3. Model for the prediction of freezing of gait in patients with early Parkinson's disease

Variables	Regression coefficient	HR (95% CI)	*p* value
PIGD score	0.438	1.549 (1.351−1.78)	0.001
Mean caudate DAT uptake	-0.622	0.537 (0.381−0.758)	0.001
CSF $A\beta_{42}$ concentration	-0.003	0.997 (0.996−0.999)	0.006

Bootstrapped results of multivariable Cox regression with all statistically significant (*p* value < 0.01) clinical and biomarker variables.

Abbreviations: $A\beta_{42}$=β-amyloid 1-42; CI=confidence interval; CSF=cerebrospinal fluid; DAT=dopamine transporter; HR=hazard ratio; PIGD=postural instability gait difficulty.

Figure 1. Kaplan-Meier estimates showing the cumulative incidence of freezing of gait in patients with early Parkinson's disease

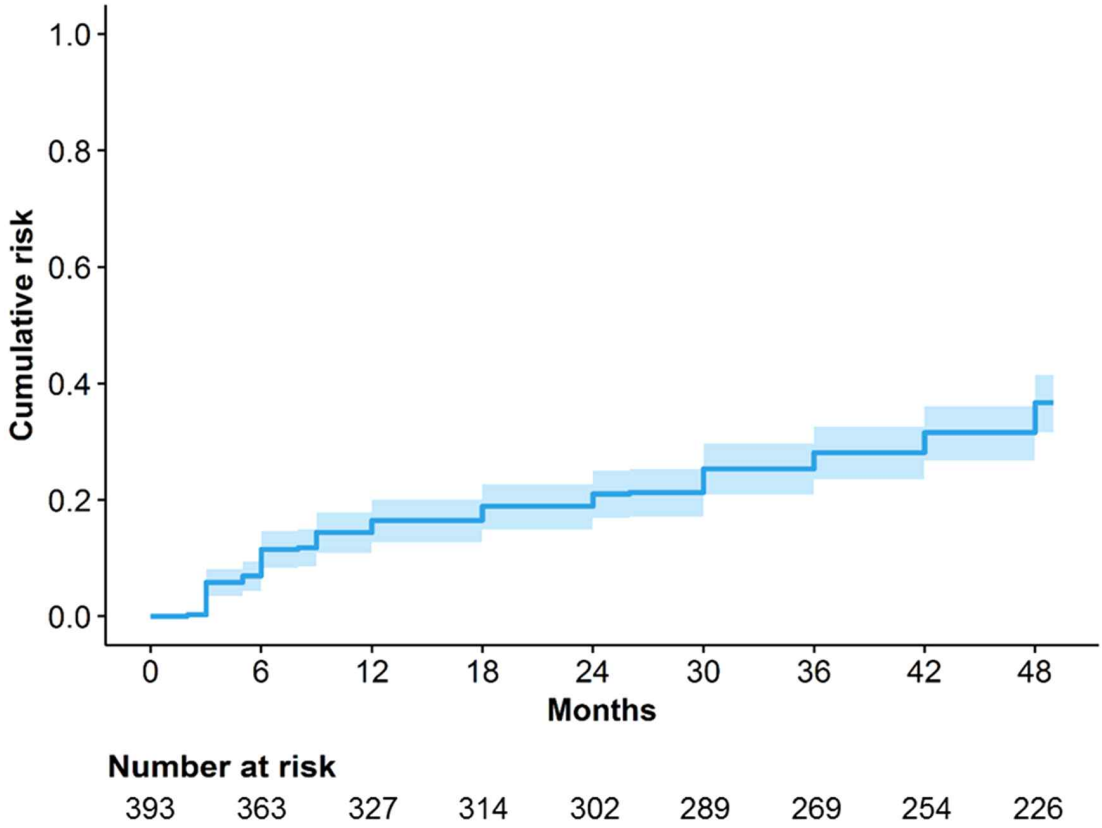
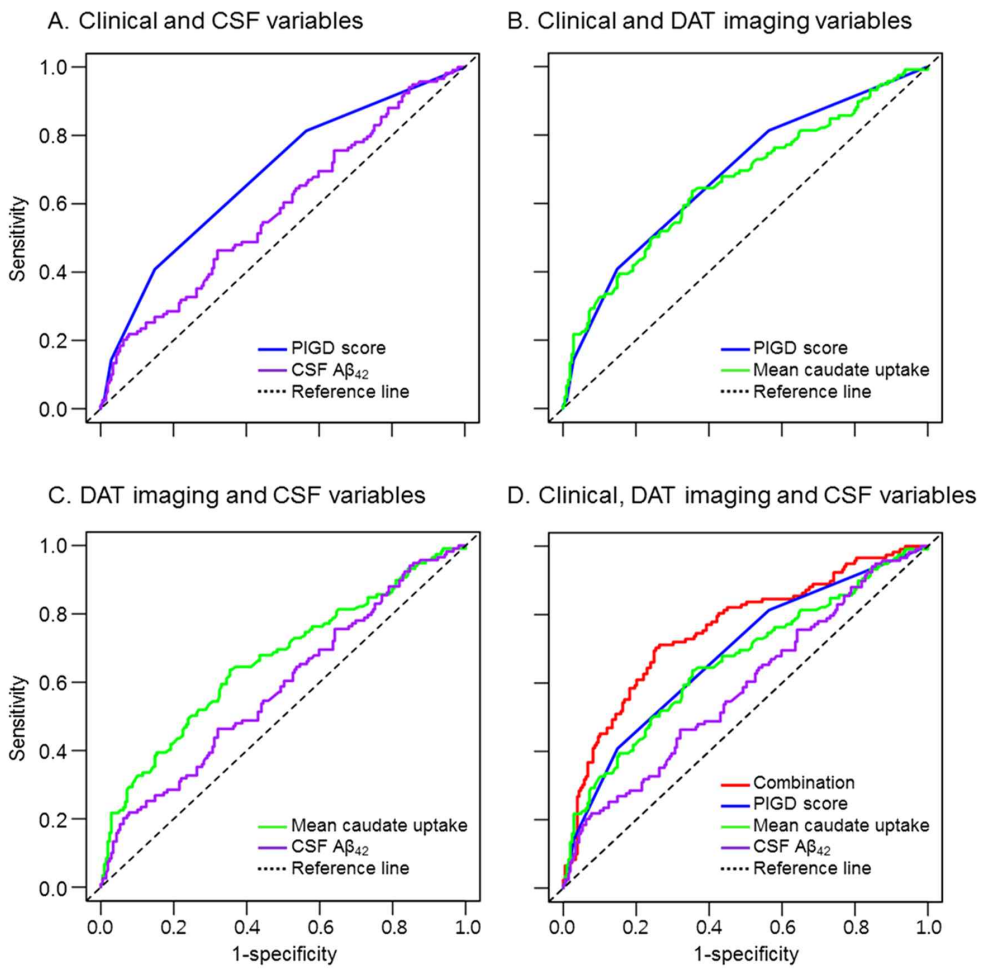


Figure 2. Time-dependent receiver operating characteristic curves for the prediction of freezing of gait at the 4-year follow-up in patients with early Parkinson's disease



Abbreviations: $A\beta_{42}$=β-amyloid 1-42; CSF=cerebrospinal fluid; DAT=dopamine transporter; PIGD=postural instability gait difficulty.

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국문초록

초기 파킨슨병에서 향후 보행동결 발생의 예측인자들: 임상적, 도파민 운반체 영상 및 뇌척수액 지표들

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서론 도파민운반체 영상 및 뇌척수액 지표들이 초기 파킨슨병 환자에서 보행동결의 예측인자일 수 있는지를 알아보고 임상지표와의 조합을 통해 향후 보행동결 발생을 어느 정도 예측할 수 있는지를 분석하였다.

방법 Parkinson's progression markers initiative (PPMI) 연구는 초기 파킨슨병 환자에서 향후 증상들의 진행을 예측하는 바이오마커를 발견하고 검증하기 위해 고안된 국제다기관 코호트 연구이다. 본 연구는 PPMI 데이터를 이용하였고 4 년까지 경과관찰한 데이터를 포함하였다. 초기 파킨슨병 환자들 중 보행동결이 없는 393 명이 연구에 포함되었다. 보행동결의 발생은 Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) 항목 2.13 또는 항목 3.11 의 답이 1 점

이상인 경우로 정의하였다. 콕스 회귀모델을 수행하여 보행동결의 예측 인자를 확인하였고 이러한 결과를 바탕으로 예측 모델을 개발하였다.

결과 평균 3.0 년 (중앙값 4.0 년)간의 추적관찰 동안 136 명의 환자들에서 보행동결이 발생하였고 보행동결의 누적발생률은 1, 2, 3, 4 년 경과관찰에서 각각 17, 21, 28 및 37%였다. 도파민운반체 영상 및 뇌척수액 지표들 중 미상핵 도파민 운반체 섭취 감소 (위험비 0.581; 95% 신뢰구간 0.408-0.827; p=0.003) 및 베타아밀로이드 1-42 (위험비 0.997; 95% 신뢰구간 0.996-0.999; p=0.009)가 보행동결의 발생과 관련이 있었다. 이외에 보행장애-자세불안 점수 (p<0.001), 남성 (p=0.046), MDS-UPDRS 운동점수 (p=0.046) 및 몬트리올 인지평가 점수 (p=0.035)가 보행동결을 예측하였다. 보행장애-자세불안 점수, 미상핵 도파민 운반체 섭취 감소 및 뇌척수액 베타아밀로이드 1-42 를 조합한 예측모델의 area under curve 는 0.755 (95% 신뢰구간 0.700 - 0.810)로 측정되었다.

결론 이 연구는 초기 파킨슨병 환자에서 선조체의 도파민결핍 및 뇌척수액 베타아밀로이드 1-42 가 향후 보행동결 발생의 예측인자인 것을 확인하였다. 또한 우리의 위험모델은 파킨슨병 진단 후 4 년 이내에 보행동결 발생을 수용 가능한 정도의 정확도로 예측하였다.

주요어: 파킨슨병; 보행동결; 뇌척수액; 예측인자
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