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SHORT COMMENTARY

Incidence and predictors of postural abnormalities in Parkinson's disease: a PPMI cohort study

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Abstract

Background Axial postural abnormalities (PA) are invalidating symptoms of Parkinson's disease (PD). Risk factors for PA are unknown.

Objectives We sought to evaluate PA incidence and risk factors over the first 4–6 years of PD.

Methods We included 441 PD patients from the Parkinson's Progression Markers Initiative (PPMI) cohort with data at diagnosis and after 4-year follow-up. PA was defined according to a posture item ≥ 2 at the Movement Disorder Society-sponsored-revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in Off therapeutic condition.

The Kruskal–Wallis test was used to compare characteristics of patients without PA ('no-PA'), with PA at disease onset ('baseline-PA'), and PA developed during follow-up ('develop-PA'). To identify predictors of PA development, univariate and multivariate Cox regression analyses were performed considering demographic, clinical and therapeutic variables.

Results 10.9% of patients showed PA at baseline and 23.7% developed PA within the first 4–6 years since diagnosis. Older age, malignant phenotype, higher MDS-UPDRS part III, Hoehn & Yahr, and dysautonomia (SCOPA-AUT) score, and lower levels of physical activity were predictors of PA development at the univariate analysis. Older age (Hazard ratio [HR] per year: 1.041) and higher MDS-UPDRS part III score (HR per point: 1.035) survived as PA development predictors in the multivariate analysis.

Conclusions PPMI cohort data show that > 30% of PD patients present PA within the first 4–6 years of disease. Older age at onset and higher motor burden are associated with a higher risk for PA development. The protective role of physical activity merits to be further investigated.

Keywords Parkinson disease · Posture · Risk factors · Prevalence · Incidence

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Introduction

Axial postural abnormalities (PA) are part of the frequent and invalidating axial motor symptoms associated with Parkinson's disease (PD) [1]. PA are typically defined as an abnormal spine flexion occurring when sitting or standing, worsened during walking, and usually resolved when lying down [1]. They proved to be a cause of falls, gait issues, loss of autonomy, and reduced quality of life (QoL) [1–3]. The severe forms of PA, namely camptocormia, Pisa syndrome and antecollis, have an estimated prevalence of about 20% during the disease course [4], with variable results according to the different methodological assessments and study designs. An advanced PD stage and greater motor symptom severity were found to be associated with the presence

of PA; however, no evidence on risk factors for the development of PA in PD can be drawn from the literature [5]. Early identification of PA and the possibility of recognizing patients at risk of developing them would help implement strategies to prevent their onset or avoid the evolution to severe spine deformities.

The Parkinson's Progression Markers Initiative (PPMI) is a multicenter study started in 2012 with the aim to follow a large cohort of PD patients since their diagnosis to gain better understanding of the disease course and its modifiers (ClincalTrials.gov NCT01141023) [6]. The PPMI study includes longitudinal and comprehensive evaluations of demographic and clinical features, as well as life habits like regular physical activity levels [6]. In this study, we rely on the PPMI study data to evaluate the incidence of PA in the first years of PD and identify the risk factors for later PA development.

Methods

Study population

We performed an analysis of the PPMI prospective, longitudinal cohort data, including PD patients within two years from the diagnosis with a positive Dopamine transporter single-photon emission computed tomography (DaT-SPECT). Patients were evaluated at baseline and longitudinally followed up every year. Among participants of the PPMI study, we included only PD patients for whom there was at least a 4-year follow-up (48 months) from the first evaluation including data for clinical assessment in the "Off" medication state.

Endpoints

Our primary endpoint was to evaluate the incidence of postural abnormalities in PD patients up to 6 years since diagnosis. The presence of axial PA was defined according to a Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) 3.13 item (posture item) ≥ 2 in in the "Off" medication state.

Secondarily, we analyzed baseline risk factors for the development of axial PA.

Data collection

We collected demographic data, encompassing age and sex, and for each PPMI visit (baseline, 1-year, 2-year, 3-year and 4-year follow-up), data on motor impairment by means of the total MDS-UPDRS part III score in the "Off" state, the item 3.13 on posture, and the Levodopa Equivalent Daily Dose (LEDD), calculated as per a validated conversion table [7], and divided per levodopa-LEDD and dopamine-agonist LEDD (DA-LEDD).

We considered the presence and severity of autonomic symptoms using the Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT) and the presence of REM behavioral sleep disorders (RBD) using the RBD screening questionnaire (RBDSQ). Moreover, the clinical phenotype of included patients was obtained using the calculator validated by Fereshtehnejad et al. to identify malignant, benign or intermediate patients, according to the presentation and severity of motor and non-motor symptoms, and available as supplementary material of the original article [8]. Physical activity was evaluated by the Physical Activity Scale for the Elderly (PASE) questionnaire, which is a scale ranging from 0 to 793 (higher scores indicating higher amount of physical activity), regarding frequency, duration, and intensity level of activity over the previous week, and including leisure, household, and occupational activities [9, 10]. The first available PASE scores in most patients (38.5%) was at one year after enrollment, so these scores were considered as the baseline PASE scores. In addition, we collected data regarding the presence or absence of osteoporosis reported in the database, as this could be a relevant comorbidity possibly influencing the presence or occurrence of axial PA.

Finally, patients were divided into three groups: those without PA at baseline and not developing PA during follow-up ('no-PA'), those with PA at baseline ('baseline-PA'), and those developing PA during follow-up ('develop-PA').

Statistical analysis

Descriptive statistics were used for continuous variables and frequency for categorical data. We calculated the incidence of development of PA over 4-year follow-up. The Kruskal–Wallis test with post hoc analyses was used for comparisons between 'no-PA', 'baseline-PA', and 'develop-PA' groups. Fisher exact test was used for categorical variables.

To identify predictors of PA development, we performed a Cox regression analysis including 'no-PA' and 'develop-PA' patients. First, we performed univariate analyses including, as dependent variables, age at baseline, sex, PD phenotype, MDS-UPDRS part III in the "Off" medication state, Hoehn and Yahr (H&Y) disease stage, total LEDD, SCOPA-AUT, RBDSQ and PASE score (all data were taken at baseline). The PASE score was also divided for leisure and household activities and inserted in another Cox model using the 2 different subscores. The model of the multivariate regression was built including as independent variables those obtaining a p value < 0.05 at the univariate analysis.

Moreover, moderate to strenuous physical activity scores at baseline and at last follow-up were calculated for each

patient by the sum of the PASE items 4, 5, and 6 and compared with the Kurskal–Wallis test. Presence of moderate-to-strenuous physical activity as per PASE item $4+5+6>0$ was also evaluated in the Cox model to verify its prediction for the development of PA.

A binary logistic regression was performed using the delta of the PASE score between the first and the last assessment to account for the possible influence of physical activity change on PA development.

Finally, a multivariate analysis of variance (MANOVA) was performed to analyze correlations of total LEDD, levodopa-LEDD, or DA-LEDD over time with the presence, absence, or development of PA.

All p values are two-tailed, with a cut-off level of significance of 0.05. Statistics was performed by the Statistical Package for the Social Sciences 27.0 for iOs (SPSS, Chicago, IL, USA).

Results

The analysis included a total of 441 PD patients (166 females). Considering all patients, baseline mean age was 61.2 ± 9.9 years, LEDD 249.5 ± 202.9 mg, and H&Y 1.6 ± 0.5. Table 1 summarizes the main demographic and clinical features of the entire cohort and of patients stratified for PA presence or development.

Incidence and prevalence of axial PA and associated features

At baseline, 10.9% of patients ($n=48$) already showed an axial PA, while 23.7% of patients without PA at onset ($n=93/393$) developed PA within the first 6 years since diagnosis, all at the last follow-up (Fig. 1). A total of 1.1% of patients ($n=5$) showed a severe PA at the 4-year follow-up, as per an MDS-UPDRS-III posture item score = 4. The overall incidence rate of axial PA occurrence in this population was 5.9 cases per 100 person-years.

Comparing 'no-PA', 'baseline-PA' and 'develop-PA' groups, we found significant differences for age at baseline ($p<0.001$), MDS-UPDRS part III scores ($p<0.001$), SCOPA-AUT ($p<0.001$), RBDSQ ($p=0.027$), PASE score ($p=0.025$), and PD phenotype ($p<0.001$). Specifically, both 'baseline-PA' and 'develop-PA' patients were older at baseline than 'no-PA' patients; motor symptom severity at baseline was significantly lower in 'no-PA' than the

Table 1 - Demographic and baseline clinical data of all PD patients enrolled

Demographic and clinical features	All patients ($n=441$)	Patients with PA at baseline ($n=48$)	Patients developing PA ($n=93$)	Patients not developing PA ($n=300$)	p values; *no-PA vs. develop-PA; ** no-PA vs. baseline-PA; *** develop-PA vs. baseline-PA
Sex: males/females (%)	275/166 (62.4/37.6%)	33/15 (68.7/31.3%)	66/27 (71/29%)	176/124 (58.7/41.3%)	* **0.038** ** 0.207 *** 0.786
Age (years)	61.2 ± 9.9 (32–85)	65.5 ± 8.6 (50–83)	64.7 ± 9.4 (32–85)	59.4 ± 9.7 (34–82)	* **< 0.001** ** **< 0.001** *** 0.714
LEDD (mg)	249.4 ± 202.9 (50–1372)	247.3 ± 174.2 (50–800)	258.8 ± 208.9 (30–1200)	246.9 ± 206 (30–1200)	* 0.660 ** 0.857 *** 0.890
MDS-UPDRS part III	20.8 ± 9.5 (4–56)	30.5 ± 11 (11–56)	22.8 ± 9 (6–46)	18.6 ± 8.1 (4–42)	* **< 0.001** ** **< 0.001** *** **< 0.001**
PD phenotype: benign/intermediate/malignant (%)	172/186/79[§] (39.3/42.6/18.1%)	10/17/20 (21.2/36.2/42.6%)	33/36/24 (35.5/38.7/25.8%)	129/133/35 (43.4/44.3/11.7%)	* **0.004** ** **< 0.001** *** **0.029**
SCOPA-AUT	14.1 ± 9.9 (0–67)	19.2 ± 10.6 (6–45)	15.9 ± 10.4 (0–51)	12.7 ± 9.3 (0–67)	* **0.005** ** **< 0.001** *** 0.053
RBDSQ	4.2 ± 2.8 (0–12)	5.2 ± 3.2 (1–12)	4.5 ± 2.8 (0–12)	3.9 ± 2.6 (0–12)	* 0.115 ** **0.015** *** 0.281
PASE	157.5 ± 103.2 (6–673)	119.8 ± 67.4 (12–253)	130.8 ± 63.8 (25–267)	174.5 ± 113.9 (6–673)	* 0.086 ** **0.017** *** 0.305

Values are expressed as mean ± standard deviation (range)

LEDD levodopa equivalent daily dose; *MDS-UPDRS* Movement Disorders Society-Unified Parkinson's Disease Rating Scale; *PD* Parkinson's disease; *SCOPA-AUT* Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire; *RBDSQ* REM behavioral sleep disorders screening questionnaire; *PASE* Physical Activity Scale for the Elderly questionnaire

[§] 4 patients were not allocated into a precise phenotype due to missing data

Bold p values indicate a statistically significant difference

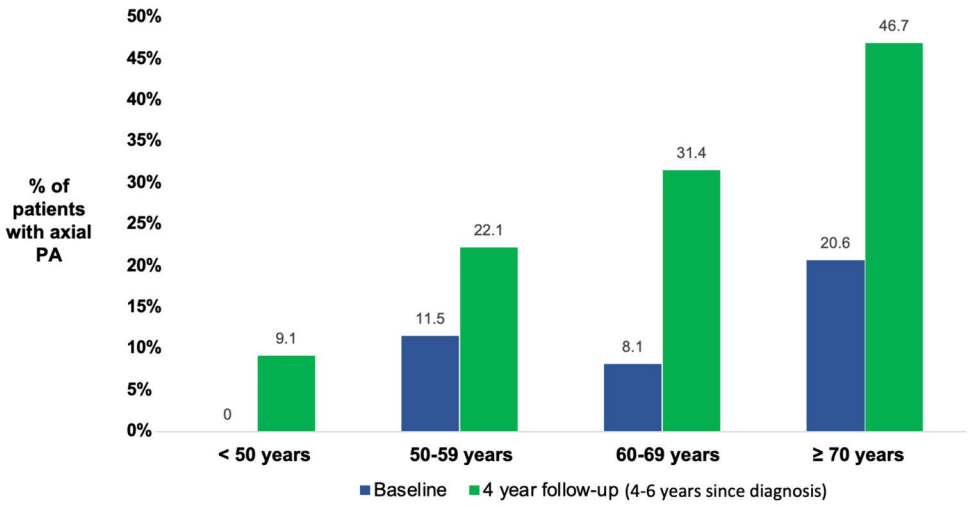

Fig. 1 Postural abnormalities in Parkinson's disease patients over the course of 4–6 years since diagnosis and stratified by age at baseline. Postural abnormalities (PA)

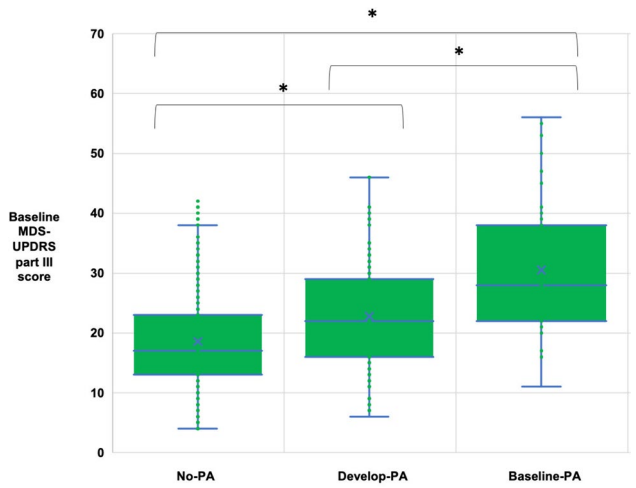

Fig. 2 The severity of motor symptoms in 'no-PA', 'baseline-PA', and 'develop-PA' groups. Movement Disorders Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) at baseline; Postural abnormalities (PA); patients without postural abnormalities over the course of 5 years from disease onset (no-PA); patients with postural abnormalities at baseline ('baseline-PA); patients who develop postural abnormalities over the course of 5 years from disease onset ('develop-PA')

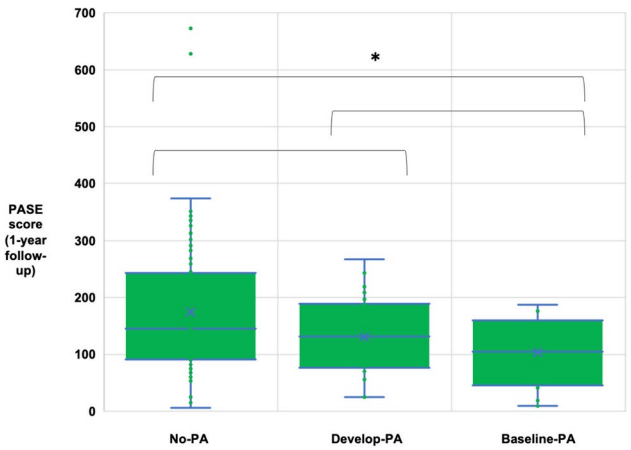

Fig. 3 Total amount of physical activity in 'no-PA', 'baseline-PA' and 'develop-PA' groups. Physical Activity Scale for the Elderly (PASE) at 1-year follow-up; Postural abnormalities (PA); patients without postural abnormalities over the course of 4–6 years since diagnosis (no-PA); patients with postural abnormalities at baseline ('baseline-PA); patients who develop postural abnormalities over the course of 5 years from disease onset ('develop-PA')

other two groups, which in turn differed for a higher score in 'baseline-PA' vs. 'develop-PA' (Fig. 2); dysautonomia was more severe in 'baseline-PA' and 'develop-PA' than 'no-PA'. RBD score was significantly higher in 'baseline-PA' than in 'no-PA', while level of physical activity was significantly lower in 'baseline-PA' if compared to 'no-PA' (Fig. 3, Table 1). The PD phenotype significantly differed between the 3 groups, with the frequency of a malignant phenotype significantly higher in 'baseline-PA' than the other two groups, which in turn differed for a higher frequency in 'develop-PA' vs. 'no-PA' (Table 1). Finally, a trend toward a significant difference was found between groups considering the amount of moderate-to-strenuous physical activity at the last follow-up, with 'baseline-PA' performing less amount of moderate-to-strenuous physical activity than 'no-PA' ($p = 0.052$).

No differences in LEDD, levodopa-LEDD, and DA-LEDD were found among groups (Supplementary Table 1).

Risk factors for the development of axial PA

At the univariate analysis, the following baseline factors resulted to be significantly associated with PA development: older age (Hazard ratio [HR] per year: 1.046, 95% Confidence Interval [CI] 1.023–1.070; $p < 0.001$), higher

MDS-UPDRS part III score (HR per point: 1.041, 95% CI 1.018–1.064; $p < 0.001$), higher H&Y stage (HR per point: 1.470, 95% CI 1.001–2.158; $p = 0.049$), higher SCOPA-AUT score (HR per point: 1.023, 95% CI 1.005–1.041; $p = 0.014$), and a malignant phenotype (HR: 1.997, 95% CI 1.180–3.378; $p = 0.010$); lower level of physical activity showed a trend toward a significant correlation (HR per point: 0.996, 95% CI 0.992–1; $p = 0.058$).

In the multivariate analysis, only older age at baseline (adjusted HR per year: 1.041, 95% CI 1.017–1.066; $p < 0.001$) and higher MDS-UPDRS part III score (adjusted HR per point: 1.035, 95% CI 1.007–1.064; $p = 0.014$) continued to be significantly associated to PA development.

Only for three patients the diagnosis of osteoporosis was reported in the dataset: all of them developed axial PA during follow-up.

Discussion

This longitudinal observational study on the PPMI cohort demonstrates that axial PA are present in 10% of PD patients at the disease onset, with an incidence of 5.9 cases per 100 person-years and a prevalence reaching 32% within the first 4–6 years since diagnosis. On the contrary, severe axial PA remains an uncommon feature in early PD [11], which aligns with diagnostic criteria for PD, as early severe axial PA typically suggest an alternative diagnosis to PD [12, 13]. Different features seem to predict the onset of axial PA within 4–6 years since diagnosis, including a malignant phenotype, a higher burden of dysautonomic symptoms, an older age at baseline, and a higher severity of motor symptoms. However, only older age at disease onset and motor symptom severity survived at the multivariate analysis, being the strongest predictors of axial PA development. Interestingly, a lower level of physical activity showed an association with the presence of axial PA and showed a trend toward the significance in predicting the development of axial PA. No influence of dopaminergic therapy, considered as total LEDD, levodopa LEDD or DA-LEDD, on the development of PA was observed.

One of the initial groundbreaking findings from our analysis was the observation of PA presence within a sizable population of newly diagnosed and early-stage PD patients. Previous studies have predominantly focused on broader PD cohorts, often including those in more advanced stages of the disease [4, 14]. However, leveraging data from the PPMI cohort enabled us to shed light on the relatively high prevalence and incidence of axial symptoms, typically associated with advanced PD stages, occurring in a significant portion of early-stage PD patients—approximately one quarter, as our analysis revealed. On a related note, we must consider that new cut-off values have been proposed for severe and mild axial PA by a MDS Task Force on Postural Abnormalities in Parkinsonism [15], identifying a new "milder" PA category. As we defined axial PA in accordance with the MDS-UPDRS 3.13 item ≥ 2 ("definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so"), it is reasonable to infer that our analysis encompasses not only severe cases of PA, but also milder manifestations.

The key role of age as a determinant of axial PA incidence aligns with previous literature based on large multicenter cross-sectional studies. Indeed, a multicenter study on over 800 patients consecutively accessing tertiary movement disorders centers found that severe axial PA were present in over 20% of cases and were associated with older age, male sex, longer disease duration, more advanced disease stage, and more severe PD symptoms [4]. Likewise, another recent cross-sectional study comparing prevalence and characteristics of PA in European and Asian PD populations found that patients with axial PA were more often male, older, with longer disease duration, more severe motor symptoms, more advanced disease stage, and a higher load of dopaminergic therapy [14].

Younger age at PD onset is a strong determinant for a higher frequency and severity of motor complications, as well as older age at onset is a predictor for more severe postural instability and motor impairment (MDS-UPDRS and H&Y), cognitive decline, and autonomic dysfunction [8]. In the multivariate analysis, we observed that the clinical phenotype, as intended malign vs. benign or intermediate, is no longer a determinant for PA development [8]. While we found that people with baseline PA or developing PA have a higher probability of being in the malignant phenotype, it seems that the role of age and motor symptoms severity is more predominant than the severity of motor and non-motor mix of symptoms in the explanation of an early development of axial PA. Intriguingly, the observation that patients with PA at diagnosis have a significantly higher probability of being in the malignant phenotype group, with a higher burden of RBD and dysautonomia, suggest a link between motor and non-motor features regulated by midline structures. Indeed, a prominent midline central nervous system pathology involvement would account for both dysautonomia, sleep disorders and also PA, as the control of posture is a rather ancient function, physiologically modulated mainly by midline structures in the brainstem (e.g., pedunculopontine nucleus and superior colliculus) and spinal cord neurons medially located in the ventral horns [16].

Another key aspect to consider interpreting our study findings is the potential role of physical activity as a protective factor for axial PA development. We observed the highest baseline level of physical activity, as per the PASE score, in patients who did not develop axial PA and the lowest in those with axial PA at diagnosis. In the regression analysis

the correlation between lower levels of physical activity and higher probability of develop PA showed a trend toward the statistically significant threshold ($p = 0.058$). These findings are even more interesting when considering that the PASE score used to assess the levels of physical activity was reported only in about 35% of the sample, probably underestimating its important role also in the prevention of axial PA after having already demonstrated in the same PPMI cohort to be associated with better gait and postural stability PD outcomes [17]. Regular aerobic training is a well-established non-pharmacological strategy for alleviating early PD motor symptoms. Our research, along with previous studies on the PPMI cohort [17], highlights a potential additional benefit of regular exercise. Specifically, it suggests that exercise may help prevent or ameliorate symptoms that are typically poorly responsive or unresponsive to levodopa, such as PA. These findings should further encourage physicians to recommend regular exercise to individuals in the early stages of PD. However, the practice of moderate-to-strenuous physical activity did not predict the development of PA over time in this cohort of early PD, although patients with PA were found to perform less amount of moderate-to-strenuous physical activity than patients without PA. If this finding is related to difficulties in performing such types of physical activity for patients with PA or is somehow related to a protective role of this kind of activity, as already highlighted in previous works [17, 18], remains to be elucidated.

Finally, despite some anecdotal cases pointed towards a potential role of dopamine agonists in the development of severe axial PA, like Pisa syndrome [19–21], and observational studies found an association between higher LEDD and the possibility of having axial PA [22], we did not find in our early cohort of PD patients a difference in the use of dopaminergic therapies between patients showing PA at baseline, those developing PA during follow-up and those who did not develop PA in the first 4–6 years of disease.

The main limitations of this study are the lack of an objective measurement of posture and the relatively short follow-up (4 years since enrollment). Moreover, the MDS-UPDRS posture item does not distinguish between antecollis, Pisa syndrome and camptocormia, allowing us to consider PA as a whole group. These shortcomings notwithstanding, we analyzed for the first time the evolution of axial PA in a large cohort of PD patients since diagnosis, allowing us to assess the incidence of axial PA in early PD, calculate the number of severe cases in the first 4–6 years since diagnosis, and identify the main demographic and clinical predictors for PA development.

In conclusion, we found an incidence of 23.6% for axial PA and a relevant role for age and motor symptom severity at PD onset for the development of PA in the following years. In addition, despite being present in a subgroup of patients, data on physical activity highly suggest its protective role against the axial PA development. Since axial PA proved to be a frequent and highly disabling motor symptom [5], we believe this information is of utmost importance to move the field toward their prevention, increasing the attention to those patients with a higher motor burden or an older age at disease onset, possibly pushing their medical and non-medical therapeutic management toward a higher intensity level.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-024-12457-3.

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Author contributions MF and CAA conceived and designed the study. CC, CL and DR performed the analyses. MZ, MGR, GI, AR, and FEP contributed to interpreting the results and wrote the first draft of the manuscript. MF, CL, DR, and CAA wrote the final version of the manuscript. All contributed to the interpretation of the results and critically revised the manuscript. All authors acknowledge full responsibility for the analyses and interpretation of the report. All authors have read and approved the final manuscript. MF and CAA are the guarantors.

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Declarations

Conflicts of interest None declared.

Ethical standards This study is based on data from 'The Parkinson's Progression Markers Initiative (PPMI)', which is a longitudinal study performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and has obtained ethic committee approval from all enrolling centers. Before entering the study, all participants gave their written informed consent. The authors of the current study are not part of the PPMI initiative, and asked and obtained access to anonymized data, as per the rules established and approved of the PPMI initiative.

Data availability statement All the data used in this study are available in the PPMI database (http://www.ppmi-info.org/data). The data supporting this study's findings are available from the corresponding author upon reasonable request.

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