Neurological Sciences (2020) 41:2883–2892
https://doi.org/10.1007/s10072-020-04404-7

ORIGINAL ARTICLE

The impact of freezing of gait on functional dependency in Parkinson's disease with regard to motor phenotype

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Received: 1 November 2019 / Accepted: 8 April 2020 / Published online: 24 April 2020

Abstract

Background and objective Freezing of gait (FOG) is a disabling symptom more frequent in Parkinson's disease (PD) patients with postural instability gait difficulty (PIGD) phenotype. The aim of this study was to determine the prevalence of self-reported FOG in a large group of PD patients as well as assess its relationship with functional dependency with regard to motor phenotype.

Methods The data correspond to the baseline evaluation of the COPPADIS-2015 study. Patients with FOG were identified as those with a score of 1 or greater on item-3 of the freezing of gait questionnaire (FOG-Q). Functional dependency was defined as a Schwab and England (S&E) ADL scale score less than 80%. PIGD and non-PIGD (tremor dominant + indeterminate) groups were considered regarding to motor phenotype.

Results Among the 689 PD patients (62.6 ± 8.9 years old, 59.8% males), 240 reported FOG (34.8%), whereas 63 presented functional dependency (9.1%). A total of 22.1% of patients with FOG presented functional dependency vs. only 2.2% of those without FOG ($p < 0.0001$). FOG was related to functional dependency (OR = 3.470; 95%CI 1.411–8.530; $p = 0.007$) after adjustment to age, gender, disease duration, daily equivalent levodopa dose, comorbidity (number of non-antiparkinsonian drugs/day), motor status (UPDRS-III), PIGD phenotype, motor complications (UPDRS-IV), NMS burden (NMSS total score), cognition (PD-CRS), and mood (BDI-II). However, according to motor phenotype, FOG was related to functional dependency only in PIGD patients (OR = 7.163; 95%CI 1.206–42.564; $p = 0.030$).

Conclusions Self-reported FOG is associated with functional dependency in PIGD but not in non-PIGD motor phenotype patients.

Keywords Activities of daily living · Freezing · Functional dependency · Gait · Parkinson's disease

Abbreviations

FOG	Freezing of gait
FOG-Q	Freezing of gait questionnaire
NMSS	Non-motor symptoms scale
PD	Parkinson's disease
PD-CRS	Parkinson's disease cognitive rating scale
PIGD	Postural instability gait difficulty
S&E	Schwab & England activities of daily living scale
TD	Tremor dominant
UPDRS	Unified Parkinson's disease rating scale

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Introduction

Currently, there is no cure for Parkinson's disease (PD). The aim of symptomatic treatment in PD is to improve, as a whole, patient's functional independence, well-being, and quality of

life (QoL). Loss of functional independence leads to caregiver burden, high resource use, institutionalization, increased risk of death, and worse QoL [1, 2]. In PD and other neurodegenerative disorders, loss of functional independence is considered an important outcome of progression [3]. Suggested predictors of functional dependency in PD patients are older age, cognitive impairment, higher severity of rigidity and bradykinesia, more severe axial symptoms, dyskinesia, and more advanced disease [4, 5]. Among the axial symptoms in PD, freezing of gait (FOG) is a frequent disabling symptom associated with more disability and worse QoL [6]. Self-reported FOG is more easily identified in advanced PD but also in patients with postural instability gait difficulty (PIGD) phenotype as well [7–9]. Defining phenotypes is needed to better understand underlying mechanisms and predict disease course. Few high-quality data on dependency are available [10] and what factors are associated with functional dependency in PD patients regarding to motor phenotype is unknown.

The aim of the present study was to analyze the prevalence of FOG and also the relationship between FOG and functional dependency in a large population of PD patients. Specifically, we analyzed the association between FOG and functional dependency with regard to motor phenotype.

Methods

PD patients from the COPPADIS cohort [11] were included in this study. Methodology about COPPADIS-2015 study can be consulted in https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-016-0548-9 [12].

The data for the present study (cross-sectional study) was obtained from the baseline evaluation of PD patients from the COPPADIS cohort between January 2016 and October 2017. All patients included were diagnosed according to UK PD Brain Bank criteria. Exclusion criteria were non-PD Parkinsonism, dementia (mini mental state examination (MMSE) < 26), age < 18 or > 75 years, inability to read or understand the questionnaires, to be receiving any advanced therapy (continuous infusion of levodopa or apomorphine, and/or with deep brain stimulation), and the presence of comorbidity, sequelae, or any disorder that could interfere with the assessment.

Information on sociodemographic aspects, factors related to PD, comorbidity, and treatment was collected. Patient baseline evaluation included motor assessment (H&Y, unified Parkinson's disease rating scale (UPDRS) part III and part IV, freezing of gait questionnaire (FOGQ)), non-motor symptoms (non-motor symptoms scale (NMSS), Parkinson's disease sleep scale (PDSS), visual analog scale-pain (VAS-Pain), visual analog fatigue scale (VAFS)), cognition (MMSE, Parkinson's disease cognitive rating scale (PD-CRS), completing a simple 16-piece puzzle), mood and neuropsychiatric symptoms (Beck Depression Inventory-II (BDI-II), Neuropsychiatric Inventory (NPI), questionnaire for impulsive-compulsive disorders in Parkinson's disease-rating scale (QUIP-RS)), disability (Schwab & England activities of daily living scale (S&E)), health-related QoL (the 39-item Parkinson's disease questionnaire (PDQ-39SI)), and global QoL (PQ-10, EUROHIS-QOL 8-item index (EUROHIS-QOL8)). In patients with motor fluctuations, the motor assessment was conducted during the OFF state (without medication in the last 12 h) and during the ON state. However, in patients without motor fluctuations, the assessment was only performed without medication (first thing in the morning without taking medication in the previous 12 h).

Patients with FOG were identified as those with a score of 1 or greater on item-3 of the FOG-Q [13, 14]. Functional dependency was defined as an S&E score less than 80% (80% = completely independent; 70% = not completely independent) [2, 4]. Different motor phenotypes were defined based on a previously published formula: tremor dominant (TD), postural instability gait difficulty (PIGD), and indeterminate [10].

Data analysis

Data were processed using SPSS 20.0 for Windows. For comparisons between patients with and without functional dependency, the Student's *t* test, Mann-Whitney *U* test, Chi-square test, or Fisher test, as appropriate, were used (distribution for variables was verified by one-sample Kolmogorov-Smirnov test). Spearman's or Pearson's correlation coefficient, as appropriate, were used for analyzing the relationship between continuous variables. Correlations were considered weak for coefficient values ≤ 0.29, moderate for values between 0.30 and 0.59, and strong for values ≥ 0.60.

For determining if FOG was related to functional dependency, a logistic regression model (functional dependency as dependent variable) was performed. The model was well-planned, as recommended by best-practice methods [15], in which known and presumably factors affecting functional independence for the activities of daily life were included as covariates: age, disease duration, motor severity (UPDRS-III), PIGD motor phenotype, motor complications (UPDRS-IV), non-motor symptoms burden (NMSS total score), cognition (PD-CRS), and mood (BDI-II). Gender, comorbidity (total number of non-antiparkinsonian medications as surrogate marker [16]), and equivalent daily dose of levodopa were also included in the model as covariates. With regard to motor phenotype, we hypothesized that FOG is associated with functional dependency in PD patients with a PIGD phenotype because FOG is a characteristic and prevalent symptom in this group, but not in patients with a phenotype different than PIGD. To test this hypothesis, the logistic regression model was checked in two subgroups: PIGD phenotype patients; non-PIGD phenotype patients (TD + indeterminate).

Hosmer–Lemeshow test was applied and adjusted R-squared was calculated for all analysis. The *p* value was considered significant when it was < 0.05.

Standard protocol approvals, registrations, and patient consents

For this study, we received approval from the appropriate local and national ethical standards committee. Written informed consents from all participants in this study were obtained before the start of the study. COPPADIS-2015 was classified by the *Agencia Española del Medicamento y Productos Sanitarios* as a post-authorization prospective follow-up study with the code COH-PAK-2014-01.

Data availability

The protocol and the statistical analysis plans are available on reasonable request. Deidentified participant data are not available for legal and ethical reasons.

Table 1 Data about motor status including gait problems and therapies in patients with vs. without functional dependency

	No functional dependency (n = 626)	Functional dependency (n = 63)	p
Age	62.3 ± 8.9	65.7 ± 8.2	0.004
Males	61.5	50.8	0.065
Disease duration (years)	5.2 ± 4.1	8.1 ± 5.2	< 0.0001
Motor phenotype	*	*	< 0.0001
-Tremoric dominant	47	23.8	*
-PIGD	36.5	65.1	*
-Indeterminate	16.5	11.1	*
Hoehn and Yahr	1.9 ± 5.2	2.5 ± 0.6	< 0.0001
-Stage 1	25	1.6	*
-Stage 2	69.1	59.1	*
-Stage 3	5	34.4	*
-Stages 4–5	0.9	4.9	*
UPDRS-III	21.6 ± 10.4	32.7 ± 12.1	< 0.0001
UPDRS-IV	1.8 ± 2.2	4.4 ± 3.3	< 0.0001
Motor fluctuations	30.1	71.4	< 0.0001
Dyskinesia	15.2	46	< 0.0001
FOG-Q	3.1 ± 3.9	10.6 ± 5.3	< 0.0001
FOG	29.9	84.1	< 0.0001
Falls	9.1	38.5	< 0.0001
Antiparkinsonian medication			
-Levodopa	70.8	92.1	< 0.0001
-Dopamine agonist	69.3	65.1	0.116
-MAO-B inhibitor	74.8	61.9	0.003
-COMT inhibitor	16.6	34.9	< 0.001
-Amantadine	7	15.9	< 0.0001
-Anticholinergic drug	3	3.2	0.329
L-dopa eq. daily dose (mg)	521.4 ± 383	915.6 ± 517.7	< 0.0001
Number of anti-PD drugs/day	2.4 ± 1.1	2.7 ± 1.4	0.042
Number of anti-PD pills/day	4.5 ± 2.7	6.5 ± 3.4	< 0.0001
Number of non-antiparkinsonian drugs/day	2.4 ± 2.3	4.6 ± 2.9	< 0.0001
Total number of pills/day	7 ± 3.8	11.2 ± 4.8	< 0.0001

Chi-squared and Mann-Whitney-Wilcoxon test were applied. The results represent percentages or mean ± SD. Data about H&Y and UPDRS-III are during the OFF state (first thing in the morning without taking medication in the previous 12 h)

COMT catechol-O-methyltransferase; *FOG-Q* freezing of gait questionnaire; *MAO-B* monoamine oxidase B; *PIGD* postural instability gait difficulty; *PD* Parkinson's disease; *UPDRS* unified Parkinson's disease rating scale

Results

Six hundred and eighty-nine PD patients (62.6 ± 8.9 years old, 59.8% males) from the COPPADIS cohort [11] were included in this study (5 patients were excluded because there was no information about S&E and/or FOG-Q scores). Of them, 34.8% ($n = 240$) and 9.1% ($n = 63$) presented FOG and functional dependency, respectively. Of the patients with functional dependency, 84.1% presented FOG vs. 29.9% of those without functional dependency ($p < 0.0001$). Of the patients with FOG, 22.1% presented functional dependency vs. 2.2% of those without FOG ($p < 0.0001$) (Table 1 and Fig. 1). Older age, longer disease duration, more advanced H&Y stage, a higher UPDRS-III score, motor complications (UPDRS-IV), higher daily levodopa equivalent dose, cognitive impairment, a greater non-motor symptoms burden (NMSS total score), depression, neuropsychiatric symptoms, sleep problems, pain, and fatigue all were related to functional dependency (Tables 1 and 2). Also, both health-related and global-perceived QoL were worse in PD patients with functional dependency vs. without functional dependency (Table 2).

With regard to motor phenotype, 44.8% of the patients presented TD, 39.2% PIGD, and 16% indeterminate. Of the patients with functional dependency, 65.1% presented a PIGD phenotype vs. 36.5% of those without functional dependency, whereas 47% of the patients without functional dependency presented a TD phenotype vs. 23.8% of the patients with functional dependency ($p < 0.0001$; Table 1). Functional dependency and FOG were related to motor phenotype, as both were the most frequently presented in PIGD phenotype patients and the least in TD phenotype patients (Fig. 2). Moderate correlation was observed between FOG-Q and S&E scales ($r = 0.56$; $p < 0.0001$). No differences were observed when this relation was analyzed with regard to motor phenotype (TD, $r = 0.54$ ($p < 0.0001$); indeterminate, $r = 0.48$; ($p < 0.0001$); PIGD, $r = 0.55$ ($p < 0.0001$)). However, a stronger correlation between FOG-Q and S&E scales was observed in the group of patients with FOG ($r = 0.50$; $p < 0.0001$) compared with those without FOG ($r = 0.39$; $p < 0.0001$) (a trend to significance; $p = 0.09$). FOG-Q score was higher in patients with FOG compared with those without FOG (8.8 ± 4.2 vs. 1.1 ± 1.3; $p < 0.0001$) as well as in PIGD phenotype patients compared with non-PIGD phenotype patients (5.5 ± 5.3 vs. 2.7 ± 3.6; $p < 0.0001$). A relationship between FOG-item 3 and functional disability was observed, so the more frequent FOG was, the more frequently the patient was functionally dependent (Fig. 3).

In the multivariable binary logistic regression analysis, FOG was related to functional dependency (OR = 3.470; 95%CI 1.411–8.530; $p = 0.007$) after adjustment to previously defined covariates in the model (Table 3). FOG-Q item 2 (gait difficulties affecting daily activities and independence) was also related to functional dependency (OR = 2.253; 95%CI 1.519–3.444; $p < 0.0001$), after adjustment to the same covariates in the model. When the analysis was performed in the subgroup of patients with PIGD phenotype, FOG was related to functional dependency (OR = 7.163; 95%CI 1.206–42.564; $p = 0.030$), but not when it was performed in those PD patients with non-PIGD phenotype (OR = 2.781; 95%CI 0.728–10.619; $p = 0.135$) (Table 3).

Discussion

The present study suggests that self-reported FOG is frequent and is associated with a functional dependency in PD patients; however, not in all cases. In patients with PIGD phenotype, to have FOG increases 7-fold the probability of presenting

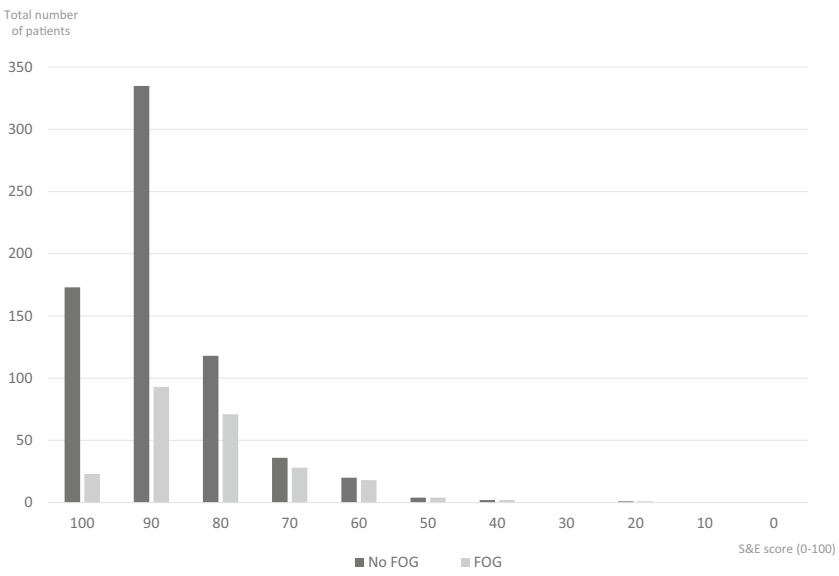

Fig. 1 Number of patients with FOG regarding to S&E score; 187 out of 626 patients without functional dependency (S&E ≥ 80) had FOG vs. 53 out of 63 with functional dependency ($p <$ 0.0001)

Table 2 Data about different non-motor symptoms and quality of life in patients with vs. without functional dependency

	No functional dependency (n = 626)	Functional dependency (n = 63)	p
MMSE	29.2 ± 1	28.8 ± 1.2	0.002
PD-CRS	92.5 ± 15.2	79.3 ± 15.8	< 0.0001
-Cognitive status:			< 0.0001
*Normal (PD-CRS > 84)	72.7	38.1	
*MCI (PD-CRS 65–84)	26.7	60.3	
*Demencia (PD-CRS ≤ 64)	0.6	1.6	
NMSS	41.5 ± 34.7	86.9 ± 44.4	< 0.0001
BDI-II	8 ± 6.8	16.1 ± 8.3	< 0.0001
-Depressive symptoms	46.8	81	< 0.0001
-Depressive disorder type*			0.002
*Major	28.9	51	
*Minor	33.3	33.3	
*Subclinical	37.8	15.7	
NPI	5.5 ± 7.4	12.8 ± 11	< 0.0001
QUIP-RS	4.2 ± 8.2	5.3 ± 9.3	0.339
PDSS	116.6 ± 23.3	98.5 ± 26.6	< 0.0001
-Patients with RBD	45.2	54.7	0.347
VAS-PAIN	2.5 ± 2.8	4.7 ± 3.3	< 0.0001
-Patients with pain	55.8	73	0.005
VASF − physical	2.7 ± 2.6	5.5 ± 2.8	< 0.0001
VASF − mental	2 ± 2.4	3.6 ± 3.1	< 0.0001
PDQ-39SI	15.3 ± 11	36.5 ± 13.4	< 0.0001
PQ-10	7.4 ± 1.4	5.8 ± 1.8	< 0.0001
EUROHIS-QOL8	3.8 ± 0.5	3.2 ± 3.8	< 0.0001

Chi-squared and Mann-Whitney-Wilcoxon test were applied (except for Fronto-subcortical and PD-CRS total scores in which Student's t test was applied because both variables had normal distribution). The results represent percentages or mean ± SD

BDI Beck Depression Inventory-II; *NMSS* non-motor symptoms scale; *NPI* Neuropsychiatric Inventory; *PD* Parkinson's disease; *PD-CRS* Parkinson's disease cognitive rating scale; *PDQ-39SI* 39-item Parkinson's disease quality of life questionnaire summary index; *PDSS* Parkinson's disease sleep scale; *QUIP-RS* questionnaire for impulsive-compulsive disorders in Parkinson's disease-rating scale; *RBD* REM behavior disorder; *UPDRS* unified Parkinson's disease rating scale; *VAFS* visual analog fatigue scale; *VAS-Pain* visual analog scale-pain

*According to DSM-IV and Judd criteria

functional dependency. On the contrary, in patients with non-PIGD phenotype, functional dependency is related to cognitive impairment, comorbidity, and greater non-motor symptoms burden, but not to FOG. Moreover, the severity in frequency of FOG (from about once a week to whenever walking) is related to the risk of having functional dependency.

Previous studies have observed that between 10 and 25% of the patients with PD are functionally dependent at the 5-year follow-up [9]. In our study, the percentage was near 10% in a population with a mean disease duration of around 5 years. A previous study reported a median duration of independent living of 5.5 years [4]. In our study, mean disease duration in the group of functionally dependent patients was 8.1 years. In the long term, it has been reported a functional dependency of 56% at 10 years [17] or 68% at 11 years [17]. Another study reported a higher risk of dependency (56% at 4 years) [18]. In general, few previous studies have analyzed functional dependency in PD as well as the selection biases and methodological differences which explain the variation in the rates of dependency rather than true population differences in dependency risk [4]. Although our study is a cross-sectional study and not a follow-up study, this is the second largest population of PD patients, after Sato et al. study [19], in which functional dependency has been analyzed [9]. Moreover, the follow-up of the COPPADIS cohort is ongoing and we will have data about functional dependency at 5 years [12].

Many factors related to a more advanced disease were associated with functional dependency in the present cohort. Patients with functional dependency were significantly older, with a longer disease duration and more advanced motor stage. Also, they presented with more frequent motor fluctuations and dyskinesia, were receiving nearly double of daily equivalent dopaminergic dose and more non-antiparkinsonian medications as a marker of a higher comorbidity [20], and had a greater non-motor symptoms burden. Except for the QUIP-RS, all scores in the scales used for assessing different non-motor symptoms indicate a worse non-motor status in functionally dependent PD patients. This is logical because patients with impulse control disorder need autonomy to carry out their activities. Cognitive impairment, neuropsychiatric symptoms, depression, sleep problems, pain, and fatigue were associated with functional dependency in our cohort. Male sex, older age, higher levels of smoking, akinesia rather than tremor, no response to L-dopa at 1 year, intellectual impairment, higher H&Y stage, and several aspects of the UPDRS scale (rigidity, bradykinesia, postural instability, dyskinesia, and total score) have been reported as prognostic factors of functional dependency development [9]. Dementia has been reported to be associated with a greater risk of functional dependency [17]. Other studies have identified MMSE as a predictor of greater disability in general [21, 22]. In our cohort, the MMSE score was significantly lower in functionally dependent patients and more than 60% of functionally dependent patients presented cognitive impairment. Also, cognitive impairment was an independent factor related to functional dependency. Another important symptom is depression because it could not only be a consequence but also a cause of motor disability in PD [23]. Interestingly, the frequency of major depression in the functional dependent PD group was higher than 40% (26/63), clearly higher than the major depression rate in this cohort (16.1%) [7] and in other reports [24].

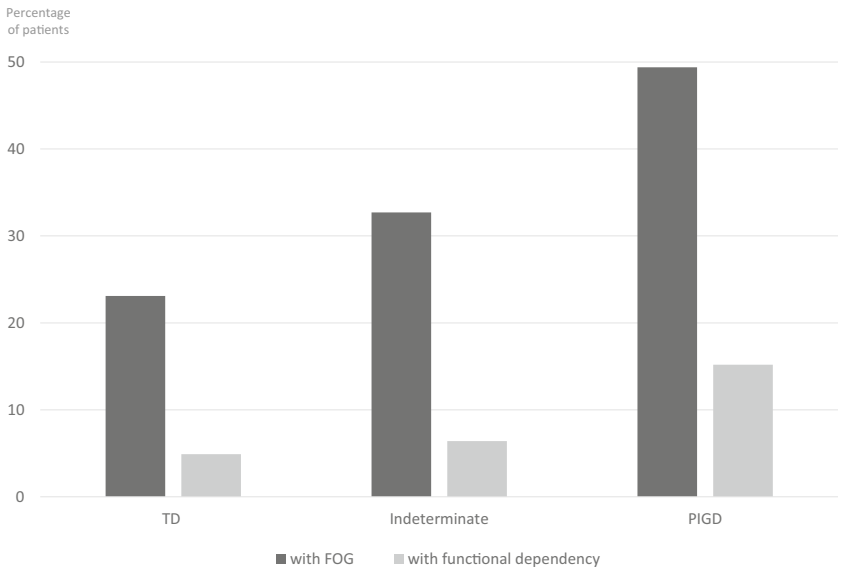

Fig. 2 Percentage of patients with FOG and functional dependency regarding to motor phenotype; the frequency was the highest in patients with PIGD phenotype ($p < 0.0001$ for both analysis)

In our cohort, 1 out of 3 patients presented self-reported FOG. Prevalence of FOG has been reported in different series: 27% [7], 32% [25], 38.2% [6], or 54.3% [10]. With regard to motor phenotype, PIGD compared with TD phenotype has been associated with rapid progression of disease and cognitive dysfunction; it is a major cause of morbidity in advanced disease, and has two important components: postural instability with falling and FOG [26]. Although tremor, as the initial motor symptom has been reported to be less likely associated with the presence of FOG, FOG can be present in PD patients with TD phenotype [26]. Indeed, more than 20% of patients with a TD phenotype from this cohort presented with FOG. In PD patients, detection of both, FOG and functional disability, is very important because both negatively impact on QoL [27, 28]. Balance confidence and FOG are associated with the mobility aspect of health-related QoL [29]. Therapies designed to improve gait problems can benefit QoL quality compared with no intervention [30]. Previously, a worse QoL was observed in those patients with FOG and gait problems from the COPPADIS cohort, which have been both reported as independent factors related to a worse QoL [31].

The present study has some limitations. Even though, this is a cross-sectional study, the follow-up of this cohort is ongoing. We will have annual data about functional dependency over the next 5 years. Also, FOG and motor phenotype data

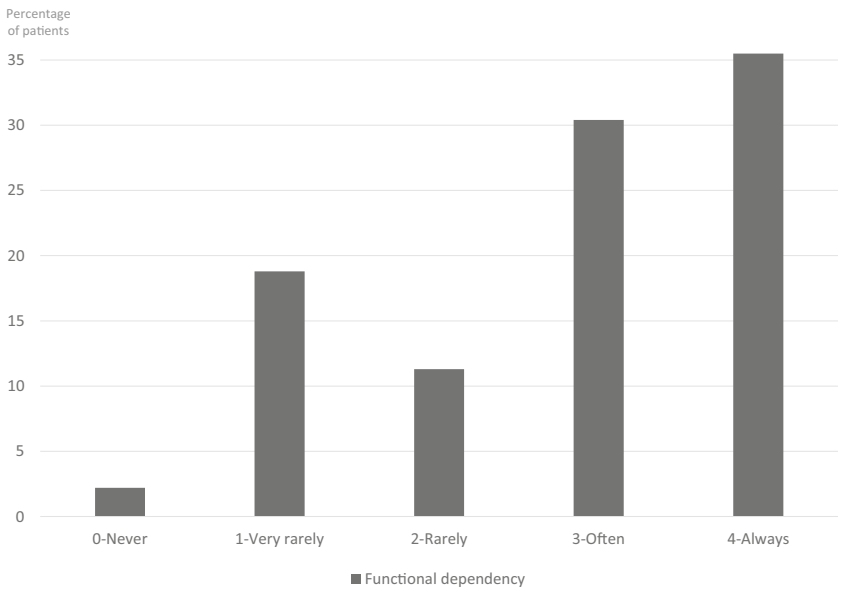

Fig. 3 Percentage of patients with functional dependency regarding FOG-Q item3. The highest frequency was observed in those patients with FOG whenever walking (always) ($p < 0.0001$)

Table 3 Binary logistic regression model about factors related to functional dependency

	OR[a]	OR[b]	OR[c]	95% IC[a]	95% IC[b]	95% IC[c]	*p*[a]	*p*[b]	*p*[c]
Age	1.013	1.022	0.968	0.961–1.068	0.944–1.107	0.890–1.052	0.636	0.587	0.438
Gender	0.684	0.326	1.692	0.331–1.414	1.104–1.022	0.514–5.568	0.305	0.054	0.387
Disease duration	1.011	1.027	0.974	0.933–1.095	0.901–1.172	0.864–1.098	0.791	0.687	0.668
L-dopa eq. daily dose (mg)	1.001	1.002	1.001	1.000–1.002	1.001–1.003	0.999–1.002	0.018	0.006	0.511
N. of non-antiparkinsonian drugs/day	1.273	1.013	1.556	1.099–1.473	0.810–1.267	1.239–1.953	0.001	0.910	<0.0001
UPDRS-III	1.030	1.028	1.005	0.996–1.064	0.981–1.076	0.947–1.067	0.082	0.247	0.861
UPDRS-IV	1.194	1.182	1.237	1.039–1.372	0.977–1.429	0.989–1.548	0.012	0.085	0.063
PIGD phenotype	1.316	N/A	N/A	0.626–2.764	N/A	N/A	0.469	N/A	N/A
FOG	3.470	7.163	2.781	1.411–8.530	1.206–42.564	0.728–10.619	**0.007**	**0.030**	0.135
NMSS	1.008	1.012	1.018	1.000–1.017	0.998–1.025	1.003–1.034	0.061	0.100	0.018
PD-CRS	0.970	0.982	0.942	0.945–0.996	0.944–1.023	0.903–0.984	0.024	0.387	0.007
BDI-II	1.069	1.133	1.020	1.016–1.126	1.034–1.242	0.949–1.095	0.010	0.008	0.595

Dependent variable: functional disability. OR and 95% IC are shown. Adjusted R-squared: a, 0.513; b, 0.630; c, 0.440; Hosmer–Lemeshow test was applied in all analysis (a, $p = 0.566$; b, $p = 0.962$; c, $p = 0.868$)

BDI-II Beck Depression Inventory-II; *FOG* freezing of gait; *N* number; *NMSS* non-motor symptoms scale; *PD-CRS* Parkinson's disease cognitive rating scale; *UPDRS* unified Parkinson's disease rating scale

[a] All cohort ($n = 698$)

[b] PD patients with PIGD motor phenotype ($n = 269$)

[c] PD patients with non-PIGD motor phenotype ($n = 418$)

will be collected at 2, 4, and 5 years [12]. FOG was defined with regard to FOG-item 3, but FOG classification as FOG only during the OFF state, FOG only during the ON state, or either in OFF and ON states was not performed [13]. Furthermore, the diagnosis of FOG was subjective, and both an insufficient or excessive diagnosis cannot be ruled out [32]. Despite this, collected data from the COPPADIS study indicates that 106 out of 483 (24.2%) patients without motor fluctuations presented FOG (vs. 64.9% of patients with motor fluctuations; $p < 0.0001$). However, functional dependency was less frequent in these patients than in those patients with FOG and motor fluctuations (15.1% vs. 27.8%; $p = 0.013$). A specific tool for assessing comorbidity, like Charlson index or others, has not been used. However, the total number of non-antiparkinsonian medications has been suggested as a useful marker of comorbidity in PD [16]. Motor subtypes are not fixed but change with progression of the disease and with treatment [33]. For some variables, the information was not collected in all cases. Finally, our sample was not fully representative of the PD population due to inclusion and exclusion criteria (i.e., age limit, no dementia, no severe comorbidities, and no second-line therapies), and a bias toward early PD exists.

In conclusion, the present study demonstrates that self-reported FOG is frequent in PD patients. It contributes to functional dependency but not in all motor PD phenotypes. In PIGD patients, FOG has to be taken account as a factor related to functional dependency, but not in non-PIGD patients (i.e., patients with TD and indeterminate phenotype). In terms of clinical applicability of these results, strategies designed to improved specific symptoms, with regard to patient's motor phenotype, could be applied with the intention to improve the functional status of the patient.

Acknowledgments We would like to thank all patients, caregivers, and all persons, companies, or institutions collaborating in this project. Especially, many thanks to Fundación Curemos el Parkinson (www.curemoselparkinson.org) and Alphabioresearch (www.alphabioresearch.com). The following are the collaborators of the COPPADIS STUDY GROUP: Adarmes Astrid D, Almeria M, Alonso Cánovas A, Alonso Frech F, Arnáiz S, Arribas S, Ascunce Vidondo A, Aguilar M, Bernardo Lambrich N, Bejr-Kasem H, Blázquez Estrada M, Botí M, Borrue C, Cabello González C, Cabo López I, Cámara Lorenzo A, Carrillo F, Carrillo Padilla FJ, Casas E, Clavero P, Cortina Fernández A, Cosgaya M, Cots Foraster A, Crespo Cuevas A, de Fábregues-Boixar O, Díez-Fairen M, Erro E, Estelrich Peyret E, Fernández Guillán N, Gámez P, Gallego M, García Campos C, García Moreno JM, Gastón I, Guillén Fopiani D, Gómez Garre MP, González Aloy J, González Ardura J, González García B, González Palmás MJ, González Toledo GR, Golpe Díaz A, Grau Solá M, Guardia G, Horta-Barba A, Idoate Calderón D, Infante J, Kulisevsky J, Kurtis M, Labandeira C, Labrador MA, Lacruz F, Lage Castro M, López Díaz LM, López Manzanares L, López Seoane B, Lucas del Pozo, Macías Y, Mata M, Martí Andres G, Martí MJ, Martínez Castrillo JC, McAfee D, Meitín MT, Menéndez González M, Méndez del Barrio C, Miranda Santiago J, Morales Casado MI, Moreno Diéguez A, Nogueira V, Novo Amado A, Novo Ponte S, Ordás C, Pagonabarraga J, Pareés I, Pascual-Sedano B, Pastor P, Pérez Fuertes A, Pérez Noguera R, Prats MA, Prieto Jurczynska C, Puente V, Pueyo Morlans M, Redondo Rafales N, Rodríguez Méndez L, Rodríguez Pérez AB, Roldán F, Ruíz De Arcos M, Ruíz Martínez J, Sánchez-Carpintero M, Sánchez Díez G, Sánchez Rodríguez A, Santacruz P, Segundo Rodríguez JC, Seijo M, Sierra Peña M, Solano Vila B, Tartari JP, Valero C, Vargas L, Villanueva C, Vives B, and Villar MD.

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Funding information Santos-García D. has received honoraria for educational presentations and/or advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, and Teva.

de Deus Fonticoba T. has received honoraria for educational presentations and advice service by Abbvie. Suárez Castro E: None. Ángel Aneiros Díaz: None. Feal Painceiras M: None. Paz González JM has received honoraria for educational presentations and/or advice service by UCB Pharma, Lundbeck, KRKA y Zambon. García Sancho C: None. Jesús S. has received honoraria from AbbVie, Bial, Merz, UCB, and Zambon. She also holds the competitive contract "Juan Rodés" supported by the Instituto de Salud Carlos III. She has received grants from the Spanish Ministry of Economy and Competitiveness (PI18/01898) and the Consejería de Salud de la Junta de Andalucía (PI-0459-2018). Mir P. has received honoraria from AbbVie, Abbott, Allergan, Bial, Merz, UCB, and Zambon. Also, he has received grants from the Spanish Ministry of Economy and Competitiveness (PI16/01575) co-founded by ISCIII (Subdirección General de Evaluación y Fomento de la Investigación), Fondo Europeo de Desarrollo Regional (FEDER), the Consejería de Economía, Innovación, Ciencia y Empleo de la Junta de Andalucía (CVI-02526, CTS-7685), the Consejería de Salud y Bienestar Social de la Junta de Andalucía (PI-0437-2012, PI-0471-2013), the Sociedad Andaluza de Neurología, the Jacques and Gloria Gossweiler Foundation, the Fundación Alicia Koplowitz, and the Fundación Mutua Madrileña. Planellas LL. has received travel bursaries grant from Abbvie. García Caldentey J. has received honoraria for educational presentations and advice service by Qualigen, Nutricia, Abbvie, Italfarmaco, UCB Pharma, Lundbeck, Zambon, Bial, and Teva. Caballol N. has received honoraria for educational presentations and advice service by Qualigen, Nutricia, Abbvie, Italfarmaco, UCB Pharma, Lundbeck, Zambon, Bial, and Teva. Legarda I. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Zambon, Bial, and Teva. Hernández Vara J. has received travel bursaries and educational grants from Abbvie and has received honoraria for educational presentations from Abbvie, Teva, Bial, Zambon, Italfarmaco, and Sanofi-Genzyme. González Aramburu I: None. Ávila Rivera MA. has received honoraria from Zambon, UCB Pharma, Qualigen, Bial, and Teva, and sponsorship from Zambon and Teva for attending conferences. Catalán MJ: None. Nogueira V: None. Álvarez Sauco M. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Zambon, Bial, and Teva. Vela L. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, and Teva. Escalante S. has received honoraria for educational presentations and advice service by Abbvie, Zambon, and Bial. Cubo E: travel grants: Abbvie, Allergan, Boston; lecturing honoraria: Abbvie, International Parkinson's disease Movement Disorder Society. Sánchez Alonso P. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, and Teva. Alonso Losada MG. has received honoraria for educational presentations and advice service by Zambon and Bial. López Ariztegui N. has received honoraria for educational presentations and advice service by Abbvie, Italfarmaco, Zambon, and Bial. Martinez-Martin P: Honoraria: from Editorial Viguera and National School of Health for lecturing in courses; International Parkinson and Movement Disorder Society for management of the Program on Rating Scales; Abbvie and Zambon for advice in clinic-epidemiological studies www.curemoselparkinson.org.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The authors received approval from the appropriate local and national ethical standards committee.

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