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Falls in ambulatory non-demented patients with Parkinson's disease

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Abstract This study aimed at determining the prevalence of falling in PD patients, to assess generic and disease-specific clinical and pharmacological factors, relationship with health-related quality of life (HR-QoL) and changes in falls from OFF to ON in patients with motor fluctuations. Six-hundred and eighty-three PD patients of the COPARK survey were evaluated (11 had missing data and were excluded from the analysis). Patients with falls were identified as those with a UPDRS Item $13 \geq 1$ in the ON condition. All patients were assessed in a standardized manner [demographics, treatments, Unified PD Rating Scale (UPDRS), Hospital Anxiety and Depression Scale, Pittsburg questionnaire and HR-QoL scales (SF36, PDQ39)]. Falling was reported by 108/672 (16 %) PD patients during the ON state and prevalence increased according to PD severity, from 5 % in Hoehn and Yahr stage 1–60 % in stage 4. Falling was significantly related to lower HR-QoL. Falling correlated with (1) generic factors such as female gender, age at the end of academic studies and diuretics consumption, (2) motor PD-specific factors including disease severity, frozen gait, difficulties when arising from a chair, dyskinesia and higher levodopa daily equivalent dose and (3) non-motor PD-specific factors such as orthostatic hypotension and hallucinations. Falling was

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more frequent in OFF than in ON in 48/74 (64 %) patients with motor fluctuations and remained unchanged in 27 patients (36 %). In summary, falling affected a significant proportion of PD patients, especially in advanced stages. It was associated with a variety of generic and PD-specific factors and was related to reduced HR-QoL.

Keywords Falls · Parkinson's disease · Gait disorders · Quality of life · Orthostatic hypotension · Hallucinations

Introduction

Falling is among the most disabling problems of Parkinson's disease (PD), affecting a substantial number of patients (Okuma 2014), and source of handicap and morbimortality (Clubb et al. 2006). Falls prevalence varies according to series. They are most frequent in the late stages of the disease (Coelho et al. 2010), but are not uncommon in the early stages (Voss et al. 2012). Predictive factors of falls are not yet fully understood, although various ones, including generic ones and PD-specific ones, have been reported (van der Marck et al. 2013). Notwithstanding, the available literature usually refers to relatively small samples of patients followed up in specialized tertiary centers, has generally focused on few specific factors rather than performing a global approach in the same population, and has not always applied multivariate analyses. Therefore, such findings cannot be generalized broadly. Moreover, little attention has been paid in the past to the possible relationship between falls and health-related quality of life (HR-QoL) in PD.

The COPARK study enrolled several hundreds of ambulatory French patients with PD, all of them being assessed systematically for demographic characteristics, motor and non-motor PD features and medications, comorbidities, co-therapies and HR-QoL. We set out this analysis to assess the relationship between falls and HRQoL in a large sample of patients with PD, generic and disease-specific factors associated with such falls and changes between the OFF and ON condition.

Methods

Population

The COPARK database included 683 ambulatory patients with PD, without dementia (MMSE $>$ 24), who had not undergone neurosurgical procedures for the treatment of PD, or who had not suffered from serious disease affecting life expectancy in the short term.

All patients were included prospectively as outpatients of public or private practicing neurologists with or without special interest in movement disorders in 32 centers from four different regions of France (see "Appendix"). The study was approved by the French national authorities and was undertaken in accordance with international guidelines. Signed informed consent was obtained from all patients in accordance with the Institutional Ethics Committee Board.

Study procedures

Each PD patient was examined by a neurologist using a standardized and structured interview. All investigators were trained during specific meetings. Socio-demographic characteristics, Mini Mental State Examination (MMSE), medical history and all drugs taken for PD at the time of the visit were recorded. UPDRS I (Mood/Cognition), II (Activities of Daily Living) and III (Motor Examination) scores were assessed in the "ON" condition. In patients with motor fluctuations (UPDRS item 39 $\geq$ 1), UPDRS II was also evaluated in "OFF." Other outcomes included the Hoehn and Yahr score, the Hospital depression and anxiety score (HADS) (Zigmond and Snaith 1983), the Pittsburg Sleep Quality Index, and two quality of life scores: a specific one, the PDQ39 (Jenkinson et al. 1995) and a generic one, the SF-36 (Ware and Sherbourne 1992).

We were therefore able to use such information to analyze simultaneously a number of (1) generic factors of falls including age, gender, age at the end of academic studies, occupation, concomitant therapies (with special focus in cardiovascular and psychotropic medications as this has been associated previously with falls) (van der Marck et al. 2013) and polypharmacy (i.e., intake of four drugs or more at the same time) (van der Marck et al. 2013), as well as comorbidities known to increase the risk of falling in the elderly (van der Marck et al. 2013); and (2) PD-specific factors such as age at PD onset, PD duration, PD severity (UPDRS II + III score), motor features (tremor [UPDRS items #16 + #20 + #21], rigidity and bradykinesia [items #22 + #23 + #24 + #25 + #26 + #31], frozen gait [item #14], walking disability [item #15 + #29], difficulties when arising from a chair [item #27], altered posture [item #28], postural instability [item #30], dyskinesia [item #32]), non-motor features (anxiety [HADS], depression [HADS], cognition [MMSE], hallucinations [UPDRS Item #2], apathy [UPDRS Item #4], daytime somnolence [PSQI item #8], orthostatic hypotension [UPDRS item #42]) and antiparkinsonian medications. Levodopa daily equivalent dose (LDED) was calculated by the usual formula (Tomlinson et al. 2010).

Evaluation of falls

Falling was explored using item #13 of the UPDRS Part II. Subjects were asked how frequently they experienced falls during the preceding month. The following options were given: 0 = "none"; 1 = "rare falling"; 2 = "occasionally, less than 1 per day"; 3 = "falls an average of one daily"; 4 = "falls more than once daily." According to the UPDRS definition, item #13 focuses on falling unrelated to freezing. This score correlates significantly with the number of falls recorded prospectively by means of a falls diary (Matinolli et al. 2011), and have been used as an outcomes in some clinical studies (Voss et al. 2012). We defined "fallers" as subjects rating more than 1 on this score, and "recurrent fallers" as those with a falling score of 2 or more.

Falling score was collected in the "ON" state in all patients. In the subgroup of patients suffering from motor fluctuations (UPDRS Item 39 scores $\geq$1), falling as well as other gait disturbances was also rated in "OFF" condition. "ON" and "OFF" were defined according to patients' perceptions, following standard and validated international definitions (Goetz et al. 2008). In patients with fall score in OFF > 0, an "OFF–ON" difference was calculated in a way that positive scores reflected improved function in "ON," whereas negative scores reflected worsened function. Percentage improvement was calculated as OFF/ON scores $\times$100.

Statistical analysis

Prevalence and their 95 % confidence intervals were calculated. Demographic and clinical characteristics are presented as frequencies and proportions. Bivariate analyses were carried out with Chi-square statistics or exact Fisher followed by logistic regression. Numerical variables' bivariate tests were dichotomized to their medians to facilitate analyses. Only variables with significant differences at the bivariate comparisons were included in the stepwise logistic models. Hosmer–Lemeshow scores were used to assess model fit. In all cases, it was higher than 0.8. Multicolinearity was absent from all models.

ON–OFF change in falls score was correlated to other variables by the Spearman rho coefficient. A multivariate ordinal regression analysis, which is an extension of logistic regression, used for outcome variables with multiple levels, was then applied. For this analysis, ON–OFF change was categorized as: 0—No; 1—improvement between 1 and 50 %; and 2—improvement between 51 and 100 %. Only variables significantly correlated with the outcome were introduced in the model.

Statistical significance was based on a 2-side test evaluated at a 0.05 level of significance. All analyzes were performed by SAS v.9.3 (North Carolina, USA).

Results

Six-hundred and eighty-three subjects were included in the study. Patients' characteristics can be found in Table 1 (left column). Thirty-nine percent were followed by movement disorder specialists, and 61 % by general neurologists.

Prevalence of falls in ON condition

Eleven patients had missing data and were excluded from this analysis. Overall Prevalence of falls was 16.1 % (95 % CI = 13.2–18.9 %). Prevalence across Hoehn and Yahr scores were as follows: 1/1.5 = 10 (15.2 %, 9.3–21.1 %); 2/2.5 = 47 (26.2 %, 22.0–30.5 %); 3 = 36 (40.5 %, 30.2–50.6 %); and 4 = 10 (58.3 %, 38.6–78.1 %). Distribution across falling scores in the whole sample was as follows: 0 = 564 patients (83.9 %); 1 = 83 (12.3 %); 2 = 21 (3.1 %); 3 = 3 (0.4 %); and 4 = 1 (0.1 %).

Relationship of falls in ON with HRQoL

Patients experiencing falls showed worse total scores and several sub-scores of both PDQ39 and SF-36 (Fig. 1). A multivariate logistic regression showed that falls were still significantly related to increased PDQ39 total score, reduced physical SF-36 score and reduced mental SF-36 score after adjusting for age and disease severity. Finally, when other variables related to gait disturbances, such as freezing of gait, walking ability, difficulties when arising from a chair, abnormal posture and postural instability were considered, falls were still directly related to total PDQ-39 score (OR, 95 % CI = 1.61, 1.01–2.58) and inversely to SF-36 physical score (0.37, 0.22–0.62) or mental score (0.52, 0.32–0.83).

The relationship between frequency of falls in ON and PDQ39, SF-36 physical or mental scores is shown in Fig. 2.

Factors related to falls

Bivariate analysis showed that a number of generic and disease-specific factors were more frequent in fallers than in non-faller patients (Table 1). A logistic regression analysis showed that fallers were more frequently women, more frequently exposed to diuretics, had lower educational level, higher UPDRS II + III score and higher UPDRS subscores referring to bradykinesia/rigidity, frozen gait, difficulties when arising from a chair, hallucinations, orthostatic hypotension and dyskinesia scores and received a higher LDED (Table 1). No difference were found according to professional status, occupation and medical history including endocrine, psychiatric, ocular, ear, cardiovascular, musculoskeletal, genitourinary or respiratory system.

Table 1 Factors related to falls in ON state

	Total simple ($n = 672$)	No falls ($n = 564$)	Falls ($n = 108$)	Multivariate OR (95 % CI)
Generic factors				
Age >67 years	338 (50.4 %)	270 (48 %)	68 (63 %)**	NR
Females	283 (42.1 %)	225 (39.9 %)	58 (53.7 %)**	1.86 (1.17–2.95)
Age at the end of academic studies >18 years	293 (43.9 %)	260 (46.5 %)	33 (30.6 %)**	0.58 (0.35–0.94)
Concomitant drugs				
Diuretics	44 (6.5 %)	28 (5 %)	16 (14.8 %)**	3.26 (1.54–6.91)
Beta-blockers	89 (13.2 %)	77 (13.7 %)	12 (11.1 %)	NI
Ca Channel blockers	65 (9.7 %)	52 (9.2 %)	13 (12 %)	NI
Drugs acting on the RAS	96 (14.3 %)	79 (14 %)	17 (15.7 %)	NI
Orthostatic hypotension	8 (1.2 %)	5 (0.9 %)	3 (2.8 %)	NI
Sedative drugs	166 (24.7 %)	135 (23.9 %)	31 (28.7 %)	NI
Opioids	45 (6.7 %)	34 (6 %)	11 (10.2 %)	NI
Antiepileptics	29 (4.3 %)	24 (4.3 %)	5 (4.6 %)	NI
Antipsychotics	11 (1.6 %)	6 (1.1 %)	5 (4.6 %)**	NR
Anxiolytics	89 (13.2 %)	73 (12.9 %)	16 (14.8 %)	NI
Hypnotics	44 (6.5 %)	39 (6.9 %)	5 (4.6 %)	NI
Antidepressants	108 (16.1 %)	79 (14 %)	29 (26.9 %)**	NR
Polypharmacy (≥5 meds)	330 (49.1 %)	255 (45.2 %)	75 (69.4 %)	NI
PD-specific factors				
Age at disease onset > 61 years	337 (50.2 %)	284 (50.4 %)	53 (49.1 %)	NI
PD duration > 5 years	337 (50.2 %)	262 (46.5 %)	75 (69.4 %)**	NR
UPDRS 2 + 3 score >26	328 (48.8 %)	247 (43.8 %)	81 (75 %)**	3.20 (1.94–3.28)
Tremor score >0	292 (43.5 %)	254 (45 %)	38 (35.2 %)	NI
Bradykinesia/rigidity score >11	328 (49 %)	252 (44.8 %)	76 (70.4 %)**	1.83 (1.08–3.12)
Freezing of gait	257 (38.2 %)	178 (31.6 %)	79 (73.1 %)**	4.20 (2.48–7.12)
Walking disability	505 (75.1 %)	409 (72.5 %)	96 (88.9 %)**	NR
Difficulties when arising from chair	227 (33.8 %)	161 (28.5 %)	66 (61.1 %)**	1.69 (1.01–2.85)
Abnormal posture	449 (66.9 %)	361 (64.1 %)	88 (81.5 %)**	NR
Posture instability	330 (49.1 %)	251 (44.5 %)	79 (73.1 %)**	NR
Dyskinesias	183 (27.2 %)	136 (24.1 %)	47 (43.5 %)**	1.83 (1.11–2.99)
Non-motor features				
Anxiety (HADS)	330 (51.1 %)	270 (49.9 %)	60 (57.1 %)	NI
Depression (HADS)	209 (32.1 %)	160 (29.3 %)	49 (46.2 %)**	NR
MMSE < 29	17 (2.5 %)	11 (2 %)	6 (5.6 %)*	NR
Hallucinations (UPDRS)	180 (26.8 %)	132 (23.4 %)	48 (44.4 %)**	2.28 (1.42–3.66)
Apathy (UPDRS)	378 (56.3 %)	301 (53.4 %)	77 (71.3 %)**	NR
Somnolence (PSQI)	222 (34.7 %)	181 (33.5 %)	51 (41.0 %)	NI
Orthostatic hypotension (UPDRS)	84 (12.5 %)	58 (10.3 %)	26 (24.1 %)**	1.84 (1.02–3.31)
Antiparkinsonian drugs				
Antimuscarinics	34 (5.1 %)	29 (5.1 %)	5 (4.6 %)	
Levodopa	544 (81 %)	448 (79.4 %)	96 (88.9 %)**	NR
Dopamine agonists	422 (62.8 %)	363 (64.4 %)	59 (54.6 %)	NI
Amantadine	61 (9.1 %)	48 (8.5 %)	13 (12 %)	NI
IMAO-b	98 (14.6 %)	86 (15.2 %)	12 (11.1 %)	NI

Table 1 continued

	Total simple ($n = 672$)	No falls ($n = 564$)	Falls ($n = 108$)	Multivariate OR (95 % CI)
Entacapone	123 (18.3 %)	103 (18.3 %)	20 (18.5 %)	NI
LDED > 500 mg/d	330 (49.1 %)	255 (45.2 %)	75 (69.4 %)**	1.70 (1.02–2.82)

Logistic regression multivariate models included only variables with significant results in the bivariate analysis

Numeric variables were dichotomized to their medians

LDED Levodopa daily equivalent dose, *RAS* Renin-Angiotensin System, *NI* Mot included in the logistic model, *NR* Not retained in the final model

* $p < 0.05$, ** $p < 0.01$ vs non-fallers (Chi-square test)

"Recurrent" fallers (i.e., falls score 2–4, $n = 25$) were more severely affected (UPDRS II + III was >26 in 92.3 vs 70.1 %, respectively, $p < 0.03$), more frequently affected by frozen gait (92.1 vs 67.6 %, $p < 0.01$) and dyskinesias (64.1 vs 37.3 %) than "rare" fallers (fall score = 1, $n = 83$). A logistic regression analysis confirmed that frozen gait and dyskinesia were independently and significantly related to recurrent falling.

Frequency of falling in OFF vs ON

Two-hundred and thirty-eight subjects reported motor fluctuations and were included in this analysis (age = 66 ± 1 years old, 41 % females, PD duration = 8.8 ± 0.3 years, UPDRS II + III score = 33.6 ± 1.1, LDED = 834 ± 28 mg/day). Ninety-six percent were on levodopa, 69 % on a dopamine agonist, 16 % on a MAO-B inhibitor, 32 % on entacapone, and 6 % on antimuscarinics.

In this subgroup of patients, falls were less frequent in ON compared to OFF conditions (22.1 vs 33.6 %, $p < 0.01$, McNemar test). Among patients with falling score >0 in OFF ($n = 74$), 27 (36.4 %) showed no changes in ON, 26 (35.1 %) improved by more than 50 %, and 22 (29.7 %) by less than 50 %. There were no patients with falling score higher in ON than in OFF.

The reduction in falls score from OFF to ON correlated with age ($r = -0.29$, $p < 0.05$), age at the end of academic studies ($r = 0.34$, $p < 0.01$), UPDRS II + III score ($r = -0.31$, $p < 0.01$), change from OFF to ON in freezing of gait ($r = 0.32$, $p < 0.01$) or walking disability ($r = -0.33$, $p < 0.01$) and with the presence of orthostatic hypotension ($r = -0.23$, $p < 0.05$). A multivariate ordinal logistic regression analysis showed that change from OFF to ON in freezing of gait was the only variable associated with the OFF-to-ON reduction in falling score.

Discussion

The present study is the largest one assessing simultaneously HRQoL and generic and disease-specific factors related to falls in PD in ambulatory PD patients not restricted to those seen at tertiary reference centers or included in randomized clinical trials. It is thus more representative of the general PD population. All patients were diagnosed and assessed in a systematic manner by neurologists trained for that survey and using validated international scales allowing simultaneous analysis a large number of generic and PD-specific factors potentially related to falls in PD. Fallers were identified using the UPDRS definition. This definition excludes frozen gait as a cause of falling, although these are two interconnected episodic phenomena (Bloem et al. 2004). Nevertheless, this definition has been validated against other falls measurements, including diaries (Matinolli et al. 2011), and has been used successfully in previous reports on that topic (Voss et al. 2012).

We observed that the prevalence of falls ranged from 15 % in mildly affected subjects to up to 58 % in the most severely affected ones with a Hoehn and Yahr score of 4. This is in line with previous reports of low fall frequency in early PD (Hiorth et al. 2013), which increases significantly in advanced PD (Coelho et al. 2010).

The relationship between falls and HR-QoL has been evaluated scarcely and incompletely in the past. Few available reports suggested that falls affect disease-specific HR-QoL, as expected intuitively (Michalowska et al. 2005; Voss et al. 2012; Wood et al. 2002). In the present study, we assessed HR-QoL using both a generic (SF-36) and a specific (PDQ39) scale. We used multivariate testing to rule out a confounding effect of other variables. Our results demonstrated a close relationship between falls and reduced HR-QoL, independently from other factors. Furthermore, when other gait disturbances were assessed with the same multivariate model, falls were still related to HR-

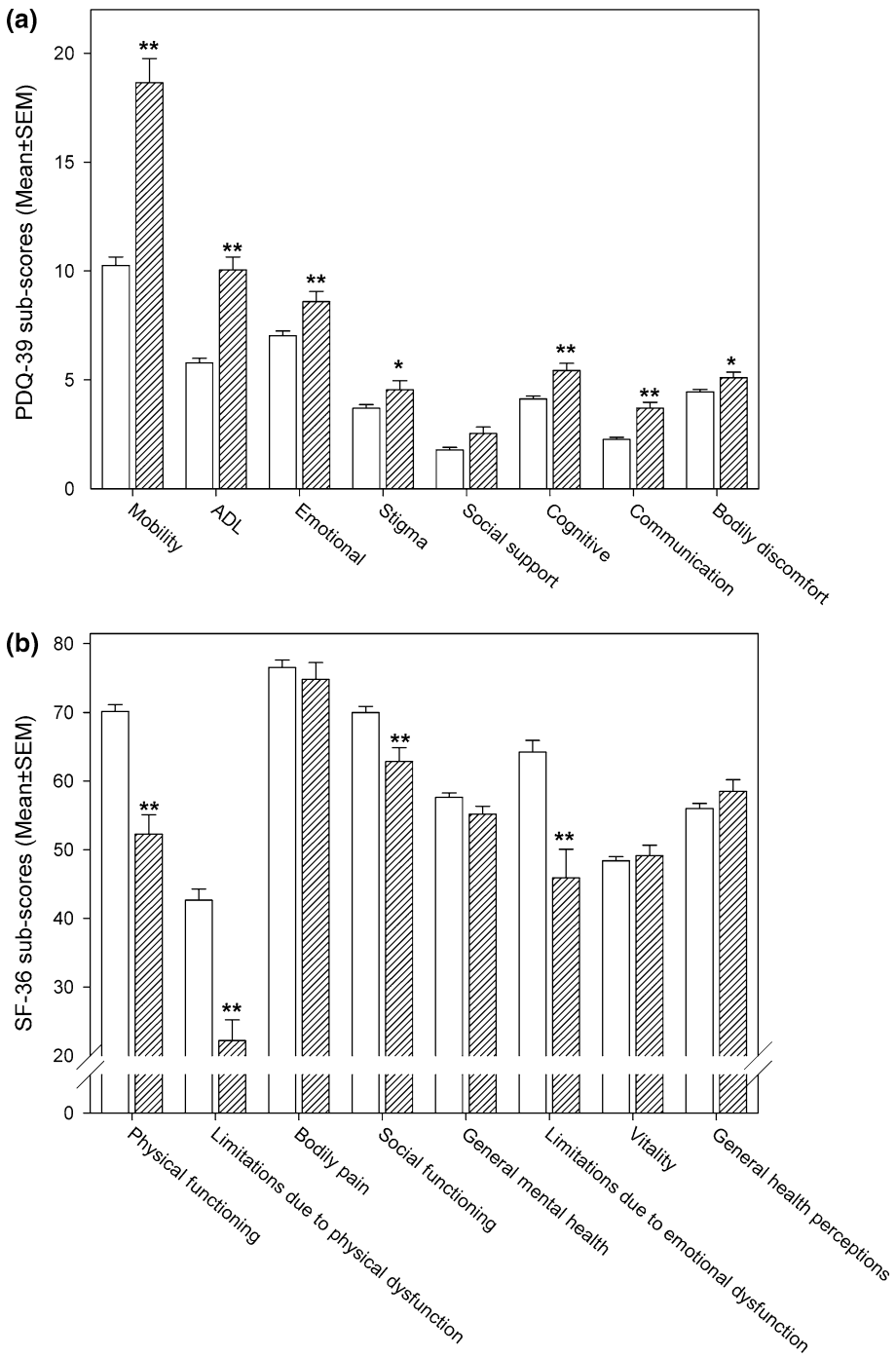

Fig. 1 PDQ-39 and SF-36 scores in patients with or without falls in ON state (in *blank* or *dashed bars*, respectively). $*p < 0.05$, $**p < 0.01$ (Student's T test with step-down Holms correction for multiple comparisons). Higher scores of the PDQ-39 and lower scores of the SF-36 scales reflect worse Quality of Life

QoL, whereas gait disturbances were no longer. This finding suggests that the effect of gait problems, for example frozen gait, on HR-QoL (Perez-Lloret et al. 2014) might be explained by patient's falls secondary to gait problems.

The present study identified several original risk factors related to falls in PD, namely hallucinations, orthostatic hypotension and dyskinesias. We found no previous report correlating falls and hallucinations in PD. This is therefore a novel finding. Interestingly, we observed that fallers received more frequently antipsychotic medications than non-fallers in our sample. Hallucinations are commonly treated with antipsychotic medications, while these drugs worsen parkinsonism and motor disability in PD. This could explain the observed link between falls and hallucinations. Inconsistent positive (Kerr et al. 2010; Michalowska et al. 2005; Rudzinska et al. 2013) and negative correlations (Matinolli et al. 2009) have been reported

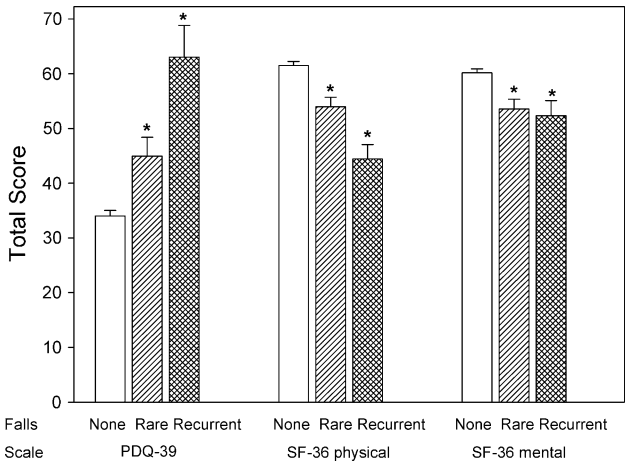

Fig. 2 PDQ-39 total score, SF-36 physical or mental scores according to the frequency of falls. *$p < 0.05$ vs patients without Falls (Dunnet post hoc test following an Analysis of Variance test). Recurrent fallers are defined as those with falling score of 2 or more. Higher scores of the PDQ-39 and lower scores of the SF-36 scales reflect worse Quality of Life

previously between falls and orthostatic hypotension in PD. Our data support such a link. Orthostatic hypotension occurs frequently in PD as a consequence of autonomic dysfunction. Orthostatic hypotension induces symptoms such as dizziness or syncope that make patients to fall. The fact that diuretics consumption, which is known to increase the risk of orthostatic hypotension in PD (Perez-Lloret et al. 2012), was also associated with falls in our series further supports the concept that orthostatic hypotension is indeed a true risk factor for falls in PD. We also found a significant correlation between falls and dyskinesia, while published data on this topic are scarce and controversial (Revilla et al. 2013; Rudzinska et al. 2013). It is conceivable that involuntary movements, such as axial choreic dyskinesia for example, may compromise balance in some PD patients and thus aggravate their risk to fall. Such a correlation is supported by the fact that dyskinesia was more common in "recurrent" fallers than in "rare" ones in our sample.

Our data confirmed that several generic factors that have been reported previously in the general population were also observed in PD patients. These included older age, female gender, younger age at the end of academic studies and diuretics, antipsychotics and antidepressants consumption. Applying multivariate statistical procedures showed that being a female increased the risk of falling, as in the general population (van der Marck et al. 2013). Differences in gait parameters between men and women (Nemanich et al. 2013) might account for such a gender difference. Lower education level has also been to correlate with unintentional injury mortality, including falls, in the general population (Burrows et al. 2012). This is in line with our observation in our PD sample. No generic comorbidities, such as cognitive impairment, arthrosis or cardiovascular disorders, or anxiolytic, hypnotic or cardiovascular co-treatments or polypharmacy was identified as related with falls in our population, although this has been reported previously (Cheng et al. 2014). Such negative findings might be due to the fact that demented patients were excluded from our sample or due to the limits of the power of the study.

Our findings also confirmed a number of risk factors that have been consistently reported previously as related to falls in PD. These include PD severity (Kerr et al. 2010; Cheng et al. 2014; Voss et al. 2012), freezing of gait (Kerr et al. 2010; Michalowska et al. 2005) and walking, postural or balance problems (Kerr et al. 2010; Rossi-Izquierdo et al. 2014; Michalowska et al. 2005). Such findings are consistent with the common concept that PD patients with greater motor disability and gait/axial/postural problems are more likely to fall. We also observed that greater akinetic-rigid scores correlated with falls, while tremor was not associated with a greater risk of fall. This is in line with the general concept that akinetic-rigid PD phenotypes have a worst prognosis than tremoric ones. As only ambulatory patients were included in this study, we could not confirm the reduction of the risk of falling in bedridden patients, as previously observed (Pickering et al. 2007). Furthermore, as our questionnaires did not collect information on previous falling, we could not assess this well known predictor factor of subsequent falls in our sample (Kerr et al. 2010; Okuma 2014; Voss et al. 2012).

The sole indicator of antiparkinsonian medications that correlated significantly with falls in our population was a greater LDED. The dose of levodopa has been reported previously as associated with falls in PD (Allen et al. 2013; Michalowska et al. 2005), and this might reflect the fact that more severe patients are more likely to fall, that the sympatholytic properties of dopaminergic medications facilitate orthostatic hypotension, or that higher doses of levodopa worsen dyskinesias.

We also observed that falling scores improved from the OFF to the ON condition in most patients who experienced motor fluctuations in our sample and that this improvement was related to an improvement in frozen gait and younger age. This is consistent with the clinical empirical observation that increasing dopaminergic treatments improves dopa-responsive OFF problems, especially in younger patients, and that the consequent improvement in gait and motor disturbances reduces the risk of falls.

In summary, the present study showed that falls are strongly related to reduced HR-QoL in PD. It identified risk factors of falls that had not been reported before or were controversial, such as hallucinations, orthostatic hypotension and dyskinesias, and confirmed more classical generic

and PD-specific ones including female gender, age at end of studies, diuretic consumption, PD severity, frozen gait, and difficulties when arising from a chair. The diversity of such factors illustrates the complexity and heterogeneity of falls in PD patients. Patients and doctors should be aware of these factors, because identification and better management of them, including motor fluctuations, orthostatic hypotension, dyskinesia, frozen gait or hallucinations, should help reducing the risk of falls for patients' well-being.

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Conflict of interest Olivier Rascol reports no disclosures, Santiago Perez-Lloret reports no disclosures, Philippe Damier reports no disclosures, Arnaud Delval reports no disclosures, Pascal Derkinderen reports no disclosures, Alain Destée reports no disclosures, Wassilios Meissner reports that a grant was received by the Bordeaux University Hospital for the project. Francois Tison reports no disclosures, Laurence Negre-Pages reports grants from the Association France-Parkinson, ADREN, Boehringer Ingelheim, Eisai, Faust Pharmaceuticals, GlaxoSmithKline, Pierre Fabre Médicaments, Solvay Pharma, Wyeth Lederlé for funding this project and that she owns stock options from LN PHARMA, which was one of the sponsors of this study.

Appendix: List of the French neurologists who participated into the patients' selection and data collection

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N. Stambouli	MD	General Hospital, Cahors
J. R. Rouane	MD	Clinique Pasteur, Toulouse
A. M. Salandini	MD	Clinique Pasteur, Toulouse
J. M. Boulesteix	MD	General Hospital, Cahors
M. Barreda	MD	Clinique Toulouse Lautrec, Castres
D. Castan	MD	General Hospital Castres
A. Ojero-Senard	MD	University Hospital Toulouse
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