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Falls in persons with Parkinson's disease: Do non-motor symptoms matter as much as motor symptoms?

Caídas en personas con enfermedad de Parkinson: ¿Los síntomas no motores importan tanto como los síntomas motores?

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ABSTRACT

Falls are common among persons with Parkinson's disease (PD). On the other hand, predicting falls is complex as there are both generic and PD-specific contributors. In particular, the role of non-motor symptoms has been less studied. **Objective:** The objective of this study was to identify the role of non-motor predictors of falling in persons with PD (PwP). **Methods:** A cross-sectional study was carried out in PwP recruited from a movement disorders clinic. Clinical and demographical data were collected. All PwP were assessed using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the Non-Motor Symptoms Scale (NMSS). Variables were assessed at the bivariate level. Significant variables were put into a logistic regression model. **Results:** A total of 179 PwP were included. Overall, 16.8% of PwP had fallen in the past 12 months, with 53.3% of them being recurrent fallers. The mean number of monthly falls was 2.5 ± 3.3. Factors associated with falling in the bivariate analysis included the disease duration, Hoehn and Yahr stage, MDS-UPDRS part I and II, postural instability/gait disturbance (PIGD) subtype, NMSS urinary domain, NMSS miscellaneous domain, and non-motor severity burden (all p-values < 0.05). After multivariate analysis, only the disease duration (p = 0.03) and PIGD (p = 0.03) remained as independent risk factors. **Conclusion:** Disease duration and the PIGD subtype were identified as relevant risk factors for falls in PwP. Non-motor symptoms appear to have a less important role as risk factors for falls.

Key words: Parkinson disease; accidental falls; risk factors; motor disorders; neurologic manifestations.

RESUMEN

Las caídas son frecuentes entre las personas con Parkinson (EP). La predicción de caídas es compleja ya que existen contribuyentes genéricos y específicos. El papel de los síntomas no motores ha sido menos estudiado. **Objetivo:** Identificar el papel de los factores no motores en caídas en personas con EP (PcP). **Métodos:** Estudio transversal en PcP reclutadas en una clínica de trastornos del movimiento. Se incluyeron datos clínicos y demográficos. Todos los PcP se evaluaron con la Escala Unificada de Enfermedad de Parkinson modificada por la Sociedad Internacional de Trastornos del Movimiento (MDS-UPDRS) y la Escala de Síntomas No Motores (NMSS). Se incluyeron variables significativas en un modelo de regresión logística. **Resultados:** Se incluyeron un total de 179 PcP. El 16.8% había presentado una caída en los últimos doce meses y el 53.3% de forma recurrente. El número medio de caídas mensuales fue de 2.5 ± 3.3. Los factores asociados con la caída en el análisis bivariado fueron la duración de la enfermedad, Hoehn e Yahr, MDS-UPDRS parte I y II, subtipo de alteración de la marcha/inestabilidad postural (PIGD), dominio urinario del NMSS, dominio misceláneo del NMSS y carga de severidad no motora (todos los valores de p < 0.05). Después del análisis multivariado, solo la duración de la enfermedad (p = 0.03) y PIGD (p = 0.03) permanecieron como un factor de riesgo independiente. **Conclusión:** La duración de la enfermedad y PIGD se identificaron como factores de riesgo para caídas. Los síntomas no motores parecen tener un papel menos relevante en las caídas.

Palabras clave: Enfermedad de Parkinson; accidentes por caídas; factores de riesgo; trastornos motores; manifestaciones neurológicas.

Falls occur frequently among persons with Parkinson's disease (PD). The reported frequency varies across studies but is estimated to be around 60%. In addition, recurrent fallers represent up to 39%[1]. Falls are also correlated with a worse quality of life, reduced life expectancy, and loss of independence[2]. Predicting risk of falling is complex due to its

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multifactorial nature. Contributing factors have been divided into generic and PD-specific, with very varied results[3]. The generic risk factors mainly include age, gender, visual impairment, cardiovascular disease and other comorbidities. The PD-specific factors include disease severity and are focused on motor symptoms such as slow mobility, freezing of gait, axial rigidity and posture instability.

On the other hand, fewer studies specifically addressing the role of non-motor symptoms (NMS) have been carried out. Most of these risk factors are known predictors of falls in the elderly, such as depression and cognitive impairment. However, the role of the full spectrum of NMS present in persons with PD (PwP) as risk factors for fall has not been addressed. As a consequence, the contribution of each independent motor and non-motor risk factor, as well as their interactions, remain only partially understood.

The objective of this study was to assess the role of NMS in the risk of falling in PwP along with motor and clinical factors.

METHODS

A cross-sectional study was carried out, including consecutive PwP attending the movement disorders clinic at the National Institute of Neurology and Neurosurgery in Mexico City. The PwP were eligible according to accepted criteria[4]. Clinical and demographic data were collected, including disease duration and fall occurrence in the past 12 months. The levodopa equivalent daily dose was calculated, as published elsewhere[5]. All examining neurologists had experience in the assessment of movement disorders. The PwP were classified as fallers (at least one fall in the past 12 months) or non-fallers. Recurrent fallers were defined as having two or more falls in the last year. The following clinical tools were applied: the Hoehn and Yahr scale (HY)[6], Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[7], and Non-Motor Symptoms Scale (NMSS)[8,9].

Also, a tremor score and a postural instability/gait disturbance (PIGD) score were used to determine the motor subtype, as published by Stebbins et al.[9]. All sections of the MDS-UPDRS were applied to evaluate non-motor experiences of daily living (part I), motor experiences of daily living (part II), motor examination (part III) and motor complications (part IV). The NMSS was used to assess both the presence and severity of non-motor symptoms. This scale evaluates 30 items grouped into nine relevant domains: cardiovascular (two items); sleep/fatigue (four items); mood/cognition (six items); perceptual problems/hallucinations (three items); attention/memory (three items); gastrointestinal tract (three items); urinary (three items); sexual function (two items); and miscellaneous items evaluating pain, olfactory alterations, weight loss, and excessive sweating. The score for each item is based on a multiple of the severity score (from 0 to 3) and the frequency score (from 1 to 4). Burden levels on the NMSS were defined for both severity (defined by the NMSS total score) and load (defined by the number of NMS declared by the PwP). Regarding NMS severity burden levels, the PwP were classified as: no NMS (score of 0), mild (score 1-20), moderate (score 21-40), severe (score 41-70) and very severe (score 71 or more)[10]. The PwP were also classified according to the NMS load burden as no NMS (0 symptoms), mild (1-5 NMS), moderate (6-9 NMS), severe (10-13 NMS) and very severe (14 or more NMS)[11].

The study was approved by the Institutional Review Board. All participants provided full written consent for participation in this study.

Statistical analysis

Normal distribution of all variables was evaluated according to the Shapiro-Wilk test. Comparisons among groups of fallers and non-fallers were conducted. Quantitative data was analyzed using the independent Student's t-test or a one-way analysis of variance (or nonparametric equivalent), as needed. Qualitative variables were compared using the X^2 test or the Fisher's Exact test, as appropriate. Variables with statistically significant differences in the bivariate analyses were put into a logistic regression model with the presence of falls in the past 12 months as the dependent variable. Variables were assessed for multicollinearity using variation inflation factors. The Hosmer-Lemeshow test was used for goodness of fit. Variance explained by the model was assessed using the Nagelkerke R-squared. A p-value of < 0.05 was considered significant. Statistical analyses were performed using the SPSS, version 17 (SPSS, Inc., Chicago, IL).

RESULTS

A total of 179 PwP were included in the study. The mean age was 64.6 ± 12.2 years and the mean disease duration was 10.4 ± 7.7 years. Distribution for disease severity was 65.4% for HY 1-2, 30.2% for HY 3 and 4.5% for HY 4 -5. The mean MDS-UPDRS part III was 26.8 ± 13.4. Regarding the motor subtype, 59.8% were classified as having PIGD, 25.7% with tremor dominant subtype, and 14.5% with indeterminate subtype. The mean levodopa equivalent daily dose was 807.1 ± 515.1 mg. Overall, 16.8% of PwP had experienced at least one fall in the past 12 months. The mean number of falls per month was 2.5 ± 3.3, with 53.3% being recurrent fallers.

A statistically significantly difference between fallers and non-fallers was found with the following variables: disease duration, disease severity (HY mild and moderate stages), MDS-UPDRS parts I, II and total scores, motor subtype (PIGD for fallers and tremor dominant for non-fallers). A full comparison of clinical and demographic variables is shown in Table 1.

Regarding severity of NMS, a statistical difference was found in the NMSS total score with fallers scoring higher. When analyzing by individual domain, fallers had a higher score in the NMSS urinary domain as well as in the NMSS miscellaneous domain. As shown in Table 2, no differences were found in the remaining domains.

Table 1. Comparison of clinical and demographic data between fallers and non-fallers.

Clinical variables[a]	Fallers (n = 30)	Non-fallers (n = 149)	p-value
Age (years)	66.7 ± 12.1	64.2 ± 12.3	0.29
Male, n (%)	19 (63.3)	91 (61.1)	0.84
Disease duration (years)	12.8 ± 8.4	7.4 ± 5.6	< 0.001
HY stage	2.7 ± 0.9	2.3 ± 0.7	0.01
HY 1-2, n (%)	13 (43.3)	104 (69.8)	0.01
HY 3, n (%)	14 (46.7)	40 (26.8)	0.03
HY 4-5, n (%)	3 (10)	5 (3.4)	0.10
MDS-UPDRS I	13.3 ± 7.1	9.7 ± 5.6	< 0.001
MDS-UPDRS II	18.4 ± 9.6	13.2 ± 10	0.01
MDS-UPDRS III	31.0 ± 13.7	25.9 ± 13.2	0.06
MDS-UPDRS IV	0.9 ± 2.5	1.23 ± 2.53	0.50
MDS-UPDRS Total	63.6 ± 22.7	50.1 ± 23	< 0.05
Motor subtype TD, n (%)	1 (3.3)	45 (30.2)	0.01
Motor subtype indeterminate, n (%)	1 (3.3)	25 (16.8)	0.06
Motor subtype PIGD n (%)	28 (93.3)	79 (53)	< 0.001
Levodopa, n (%)	27 (90)	120 (80.5)	0.29
Levodopa equivalent daily dose, mg	954.90 ± 652.50	777.33 ± 479.99	0.08

HY: Hoehn and Yahr; MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; TD: tremor dominant; PIGD: postural instability and gait disorder.

Table 2. Comparison of non-motor symptoms between groups [a].

Variables	Fallers (n = 30)	Non-fallers (n = 149)	p-value
NMSS Cardiovascular	1.9 ± 4.5	0.9 ± 2.4	0.23
NMSS Sleep/fatigue	11 ± 13.5	6.1 ± 10.6	0.07
NMSS Mood/cognition	12.0 ± 19.0	6.7 ± 13.4	0.16
NMSS Perceptual/hallucinations	3.1 ± 9.0	0.8 ± 2.9	0.18
NMSS Attention/memory	6.2 ± 11.4	3.0 ± 6.7	0.15
NMSS Gastrointestinal	5.3 ± 5.5	4.0 ± 5.9	0.25
NMSS Urinary	10.8 ± 12.6	5.7 ± 8.9	0.04
NMSS Sexual function	0.8 ± 4.4	1.8 ± 11.2	0.65
NMSS Miscellaneous	5.0 ± 5.4	2.4 ± 5.2	0.02
NMSS Total Score	56.1 ± 47.0	31.5 ± 33.1	0.01
NMS Load burden			
No NMS	0	0	--
Mild (1–5)	2 (6.7%)	19 (12.8%)	0.14
Moderate (6–9)	3 (10.0%)	33 (22.1%)	0.13
Severe (10–13)	10 (33.3%)	40 (26.9%)	0.47
Very severe (> 13)	15 (50.0%)	57 (38.2%)	0.23
NMS Severity burden			
No NMS	0	0	--
Mild (1–20)	8 (26.7%)	73 (49%)	0.02
Moderate (21–40)	9 (30.0%)	39 (26.2%)	0.66
Severe (41–70)	1 (3.3%)	13 (8.7%)	0.32
Very Severe (> 70)	12 (40.0%)	24 (16.1%)	0.01

NMSS: Non-Motor Symptom Scale; NMS: non-motor symptoms. [a]Data are mean ± SD; or absolute numbers and percentages

After categorizing by NMS severity burden, fallers had a "very severe" burden while non-fallers had a "mild" burden (Table 2). On the other hand, no differences were found when comparing the NMS load burden between groups (17.4 ± 8.7 among fallers, 14.8 ± 9.3 among non-fallers; p = 0.16).

A logistic regression model was designed using variables with differences in the bivariate analyses. The MDS-UPDRS total score was not included in the model to avoid multicollinearity (variation inflation factors = 5.1) with MDS-UPDRS parts I and II scores. In addition, a new MDS-UPDRS part I score, subtracting items 1.9 (pain) and item 1.10 (urinary problems), was calculated to avoid collinearity with the NMSS domains evaluating these symptoms. This new MDS-UPDRS part I partial score maintained a statistically significant difference between groups (p = 0.01).

Similarly, the NMSS total was also excluded due to multicollinearity (variation inflation factors = 5.03) with the genitourinary and miscellaneous domains. No significant multicollinearity was found between the remaining variables. The variables included in the model were disease duration, HY stage, motor subtype, MDS-UPDRS part I score, MDS-UPDRS part II score, NMSS genitourinary score, NMSS miscellaneous score, and NMS severity burden. After the regression analysis, only the disease duration and PIGD subtype remained significant. Data derived from multivariate analysis are shown in Table 3. The Hosmer-Lemeshow test showed goodness of fit (χ^2 = 7.12, df = 8, p = 0.524) and the Nagelkerke R-squared was 0.32. This multivariate model correctly classified the outcome for 84.9% of the cases.

DISCUSSION

The proportion of fallers among our sample was very low (16.8%). Prospective studies have reported falling frequency at three months follow-up to range between 36% and 59%[12], whereas retrospective studies have reported 31% and 32.9% in the previous month and year, respectively[13,14]. Interestingly, some studies have assessed falling frequency in both prospective and retrospective ways with mixed results. In one study the incidence of falls reported by anamnesis (retrospective analysis) did not differ from the prospective assessment after one year[15]. Another study found that 79.7% of participants fell over 54 months compared with 26.2% of participants who reported retrospective falls at baseline[16]. The low proportion of fallers in our sample could partially be explained by underrepresentation of advanced forms of the disease, with only 4.5% being at HY 4–5 stages.

The difficulty designing accurate fall prediction models highlights the complexity of fall risk. Generic age-related risk factors are well known and include age, female sex, polypharmacy, autonomic dysfunction, arthrosis, visual impairment, and depression, among others[3]. Many prediction models have been proposed with varying results. A meta-analysis of six prospective studies (n = 473) found that the strongest predictor of falling was prior falls in the preceding year. Although relevant, recurrent falling is of limited use for prevention models and was not further evaluated in our study. This large meta-analysis also failed to identify disease severity as a significant predictor of falls[12].

In our study, the severity of motor symptoms failed to predict falling. This finding is consistent with other studies that have failed to show motor variables as independent predictors of falls[13,17]. The only independent predictor statistically significant at the multivariate level was the disease duration and the PIGD subtype. The PIGD as a risk factor has already been reported[18] and is consistent with other studies that have identified slow mobility[19], freezing of gait, posture, postural instability[20], and axial rigidity[21] as significant predictors. Conversely, the PIGD subtype has been associated with greater severity of nondopaminergic (mainly cholinergic) symptoms[22] and greater cognitive impairment[23], which may account for an increased risk of falling. The frequency of the PIGD subtype in our study was almost 60%, which is in line with the 64% reported by Stebbins et al.[9]. Nevertheless, it is relevant to consider that it has been proven that the motor

Table 3. Multivariate logistic regression model for predicting falls in people with Parkinson's disease.

Variable	B	Exp (B)	95% CI	p-value
Disease duration (years)	0.06	1.06	1.01 - 1.11	0.03
MDS-UPDRS I partial score *	0.09	1.09	0.98 - 1.23	0.12
MDS-UPDRS II	-0.03	0.97	0.93 - 1.03	0.32
HY stage	0.48	1.62	0.90 - 2.9	0.11
PIGD Subtype	2.33	10.25	1.25 - 83	0.03
TD subtype	0.18	1.19	0.06 - 24.6	0.91
NMSS urinary	0.02	1.02	0.97 - 1.07	0.50
NMSS miscellaneous	0.05	1.05	0.98 - 1.14	0.19
Mild NMS severity burden	0.14	1.15	0.21 - 6.44	0.88
Very severe NMS severity burden	0.14	0.87	0.16 - 1.49	0.88

MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr stage; PIGD: postural instability and gait disorder; TD: tremor dominant; NMSS: Non-Motor Symptoms Scale; NMS: non-motor symptoms; * MDS-UPDRS part I score minus items 1.9 and 1.10.

subtype is not stable and tremor dominant/PIGD subtypes can shift category over time[24]. Moreover, Alvarado-Franco et al. reported a shift from tremor dominant to PIGD subtype in Mexican PwP, increasing from 21% to 42% over a six-year follow-up[25]. After multivariate analysis, both the disease duration and PIGD subtype remained as statistically significant predictors but this finding needs further confirmation through a prospective design. In addition, the disease duration in our sample was around eight years and should be considered when interpreting the results.

Motor fluctuations are among the least-consistent predictors. Some authors have suggested an association between dyskinesia and falls[17], whereas others failed to prove this. The same was true for wearing off, with some suggesting association[26] and others with inconclusive results[17]. In our sample, no difference was found in the MDS-UPDRS part IV, which assesses both wearing off and dyskinesia.

On the other hand, the association of NMS and falling risk has scarcely been explored. Some studies have associated falling risk with cognitive impairment[19,27], rapid eye movement sleep behavioral disorders[13,28], autonomic dysfunction[29], depression[30], cardiovascular comorbidity[31] and urinary incontinence[14]. In our study, in the NMSS genitourinary domain, miscellaneous and total scores were higher among fallers, although none of these variables were shown to be independent predictors within the regression model. One possible explanation for the association between urinary symptoms and falls is through dysautonomia, which may lead to falls. However, in our study, the NMSS cardiovascular domain was not associated with falling. Another possible explanation that needs further study is nocturia, which is often the prevailing factor leading to nighttime falls[32]. The miscellaneous domain evaluates several NMS, including pain, change in taste or smell, change in weight and excessive sweating. Of these items, excessive sweating may be associated with dysautonomia. Weight change also has some theoretical foundation, since a higher body mass index has been linked to falling risk[33]. Unfortunately, the heterogeneity of this domain does not allow strong conclusions. A major limitation of our study was the fact that the patients were not evaluated according to specific recommended tools[34,35,36] for all NMS, particularly in the case of neuropsychiatric symptoms; therefore screening may not have been ideal.

To the best of our knowledge, this is the first study to explore the NMSS severity and load burdens as potential predictors of falls. We theorized that the number and severity of accumulating NMS could significantly contribute to falling risk. Interestingly, the NMSS severity burden was higher among fallers but did not prove to be an independent predictor after multivariate analysis.

Our study has other limitations. A retrospective assessment of previous history of falls may not be reliable for identifying fall predictors and is subject to recall bias. Nonetheless, similar estimates of fall incidences have been reported using both retrospective and prospective methodologies[15]. As mentioned before, a referral bias was present with the under-representation of PwP in the more severe stages of the disease; therefore, our results may not be reproducible in patients with advanced stages of the disease. This is particularly relevant as fall frequency is thought to have an inverted U-shaped curve mediated by ambulatory activity that decreases as disease severity increases[37]. Lastly, our model showed an adequate goodness of fit but found that the variance was lower than that reported by other authors[38]. This may be due to the complex multifactorial nature of falling prediction. Other models with higher predictive values included different variables including physical activity[39], past falling and fear of falling[40], the retropulsion test and tandem gait[41]. These variables were not individually assessed although the retropulsion test and gait were included in the MDS-UPDRS part III and used to classify PwP within the motor subtypes.

In conclusion, our study identified several motor and non-motor symptoms as factors associated with falls in PwP, but only the disease duration and PIGD remained as independent predictors after multivariate analysis. These findings suggest a more intensive approach in fall prevention among PwP with this subtype. On the other hand, longitudinal studies with PwP in early disease stages are warranted.

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