Artículo original

Prevalence of non-motor fluctuations in Parkinson's disease in an outpatient tertiary referral center

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Abstract

Introduction: motor fluctuations in Parkinson's disease (PD) have been extensively studied, but much less is known about the behavior of non-motor symptoms.
Objective: the objective of the present study is to characterize the non-motor fluctuations in patients with Parkinson's disease attending an outpatient tertiary referral center, and correlating them with the main clinical features.
Methods: patients with a diagnosis of Parkinson's disease were included. The presence of non-motor symptoms was determined with the MDS-UPDRS Part 1A, and the severity and frequency of these symptoms were assessed with the Non-Motor Symptom Scale (NMSS). The Non-Motor Fluctuations Questionnaire (NMFQ) of the Spanish Society of Neurology was applied by independent evaluators, blinded to the motor assessment, to determine the fluctuating pattern of these features. Independent evaluators applied the Parkinson's Disease Questionnaire Short Form (PDQ-8) to assess patients' quality of life.
Results: a total of 50 patients were included. Mean MDS-UPDRS IA score was 3.58 ± 3.28, and mean NMSS score was 58.29 ± 54.73. The most severe non-motor symptom was pain, followed by anxiety and depression. Twenty-six patients (52%) had at least one non-motor symptom with a fluctuating pattern. The most common fluctuating symptom was hallucinations (66.7%), followed by pain and paresthesias (44.4% each). Although there was a tendency for non-motor symptoms to present more frequently during off periods, no statistically significant results were found.
Conclusion: non-motor fluctuations are frequent. Our findings suggest non-motor fluctuations are independent of motor fluctuations and pharmacological treatment.

***Keywords:** Parkinson's disease, non-motor symptoms, fluctuations, pharmacological treatment.*

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Prevalencia de fluctuaciones no motores en enfermedad de Parkinson en un centro terciario de referencia para pacientes ambulatorios

Resumen

Introducción: las fluctuaciones motoras en la enfermedad de Parkinson (EP) han sido ampliamente estudiadas; sin embargo, se conoce mucho menos sobre el comportamiento de los síntomas no motores.
Objetivo: el objetivo del presente estudio es caracterizar las fluctuaciones no motoras en pacientes con enfermedad de Parkinson que asisten a un centro terciario de referencia para pacientes, y la correlación con las principales características clínicas.
Métodos: se incluyeron pacientes con diagnóstico de enfermedad de Parkinson. La presencia de síntomas no motores se determinó mediante la parte 1A del MDS-UPDRS. La gravedad y la frecuencia de estos síntomas no motores se evaluaron utilizando la escala de síntomas no motores (NMSS). El Cuestionario Las fluctuaciones no motores (NMFQ) de la Sociedad Española de Neurología se aplicó por evaluadores independientes, cegados a la evaluación motora, para determinar el patrón fluctuante de estas características. Los evaluadores independientes aplicaron adicionalmente el Cuestionario de la Enfermedad de Parkinson (PDQ-8) para evaluar la calidad de vida del paciente.
Resultados: se incluyeron un total de 50 pacientes. La media de puntuación de MDS-UPDRS IA fue de 3.58 ± 3.28, y la media de puntuación de NMSS fue 58.29 ± 54.73. El síntoma no motor más grave fue el dolor, seguido de la ansiedad y la depresión. Veintiséis pacientes (52%) tuvieron al menos un síntoma no motor con un patrón fluctuante. El síntoma fluctuante más común fueron las alucinaciones (66,7%), seguidos por el dolor y parestesias (44,4% en cada caso). Aunque existió una tendencia a que los síntomas no motores se presentaran con mayor frecuencia durante los periodos *off*, no se obtuvieron resultados estadísticamente significativos.
Conclusiones: las fluctuaciones no motoras son frecuentes. Nuestros hallazgos sugieren fluctuaciones no motores son independientes de las fluctuaciones motoras y tratamiento farmacológico.

Palabras clave: *Enfermedad de parkinson, síntomas no motores, fluctuaciones, tratamiento farmacológico*

Introduction

Motor fluctuations in Parkinson's disease (PD) have been extensively studied, and contrary to what was previously thought, they can begin relatively early in the course of the treatment[1,2]. Much less is known about the behavior of non-motor symptoms in relationship with the on period (with medication effect) and off period (without medication effect). While some authors have suggested these non-motor fluctuations closely correlate with motor fluctuations[3-5], the heterogeneity of study designs and different populations make the data difficult to interpret and the issue remains controversial.

Non-motor symptoms have a high impact on quality of life[6], and their burden can actually be more disabling than motor features[7]. However, the fluctuating nature of these symptoms appears to have a less robust role than the presence of them 3. Even though extensive research has being conducted regarding the treatment of non-motor symptoms, the management of their fluctuations is still unclear. If non-motor fluctuations are in fact not associated with motor ones, a different therapeutic approach should be sought.

The aim of this study was to characterize the non-motor fluctuations in PD patients attending an outpatient tertiary referral center, and correlating them with the main clinical features.

Materials and methods

Subjects

This is a sub-study of the Mexican Registry of Parkinson's Disease (ReMePARK)[8], which is a prospective cohort of PD patients. For this sub-study consecutive patients attending the Movement Disorder Clinic at the National Institute of Neurology and Neurosurgery in Mexico City, with a diagnosis of PD according to the UK Parkinson's Disease Society Brain Bank criteria[9] were recruited between June 23th and August 1rst 2014. All patients gave full written consent for participation as dictated by the local Ethics Committee. The study was approved by the Institutional Review Board.

Data collection

All patients were evaluated by a neurologist with expertise in Movement Disorders. Demographic and clinical data were recorded, and Levodopa equivalent daily dose (LEDD) was calculated[10]. The Spanish version of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[11] was applied to all subjects. The presence of non-motor symptoms was determined with the MDS-UPDRS Part 1A, and the severity and frequency of these symptoms were assessed with the Non-Motor Symptom Scale (NMSS)[12]. The Non-Motor Fluctuations Questionnaire (NMFQ) of the Spanish Society of Neurology was applied by independent evaluators, blinded to the motor assessment, to determine the fluctuating pattern of these features[13].

The NMFQ is an instrument developed as a simple tool to establish the presence of fluctuations in the most common non-motor symptoms of PD. It is applied by a clinician as a dichotomic 8-item questionnaire (yes/no answers), first investigating the presence of non-motor symptoms during the last month, and then asking if those symptoms were present during on or off periods (or both).
Finally, independent evaluators applied the Parkinson's Disease Questionnaire Short Form (PDQ-8)[14] to assess patients' quality of life. All information was obtained directly from patients or with the help of caregivers when needed.

Statistical analysis

Data was expressed as means and standard deviations, or frequencies and percentages, as appropriate. Normality was tested for all variables. The presence of non-motor fluctuations was compared with PDQ-8 and KPDPS scores using independent Student's T tests. Relationship of motor fluctuations, antiparkinsonian therapies and LEDD with non-motor fluctuations was assessed using Pearson's chi-

squared tests. A p level of < 0.05 was considered significant. Statistical analyses were performed using SPSS, version[17] (SPSS, Inc., Chicago Illinois).

Results

A total of 50 patients were included; table 1 shows the clinical and demographic data. A total of 24% (n = 12) of patients experienced motor fluctuations. Mean MDS-UPDRS IA score was 3.58 ± 3.28, and mean NMSS score was 58.29 ± 54.73; complete subscores are detailed in table 2. The most severe non-motor symptom was pain, followed by anxiety and depression. 52% of patients (n = 26) had at least one non-motor symptom with a fluctuating pattern. The most common fluctuating symptom was hallucinations (66.7%), followed by pain and paresthesias (44.4% each). Prevalence of all non-motor fluctuations is described in table 3. Although there was a tendency for non-motor symptoms to present more frequently during off periods, no consistent trends were found.

Table 1. Patient demographics and clinical data*

Variable	Value
Age (years)	64.8 ± 11.7*
Male gender (%)	26 (52%)
Disease duration (years)	6.2 ± 4.4*
Currently on dopaminergic treatment (%)	41 (82%)
LEDD (mg)	578.6 ± 469.9*
MDS-UPDRS Part II	12.4 ± 9.5*
MDS-UPDRS Part III	29.9 ± 14.1*
MDS-UPDRS Part IV	1.7 ± 2.8*
MDS-UPDRS Total Score	55.5 ± 26.3*
Mild disease (H&Y 1-2) (%)	29 (58%)
Moderate disease (H&Y 3) (%)	15 (30%)
Severe disease (H&Y 4-5) (%)	6 (12%)
PDQ-8	9.4 ± 7.8*

H&Y: Hoehn and Yahr staging. LEDD: Levodopa equivalent daily dose. MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale. PDQ-8: Parkinson's Disease Questionnaire Short Form. *Mean ± Standard Deviation.

Student's T tests did not show an association between non-motor fluctuations and PDQ-8 scores. Similarly, Pearson's chi-squared tests did not show a correlation between the presence of motor fluctuations and any of the non-motor fluctuations, nor did the use of levodopa, dopamine agonists, monoamine oxidase B inhibitors, Catechol-O-Methyl transferase inhibitors or LEDD.

Table 2. Non-motor symptoms according to MDS-UPDRS IA and NMSS scores.

Non-motor symptom	MDS-UPDRS IA	NMSS
Cognitive impairment	0.84 ± 0.87	NA
Depression	0.96 ± 1.18	3.76 ± 4.89
Apathy	0.30 ± 0.76	2.26 ± 4.16
Hallucinations	0.28 ± 0.73	0.32 ± 1.33
Anxiety	1.00 ± 1.18	3.74 ± 4.62
Pain	NA	4.34 ± 5.09
Excessive sweating	NA	2.72 ± 4.37
Fatigue	NA	2.84 ± 4.08
Dopamine dysregulation syndrome	0.20 ± 0.64	NA

NA. Not Available. NMSS: Non-motor Symptom Scale. MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale

Table 3. Prevalence of non-motor fluctuations.

Non-motor symptom	Total patients	Patients with a fluctuation pattern	Prevalence of fluctuations
Depression	23 (46%)	8 (16%)	34.8%
Apathy	14 (28%)	5 (10%)	35.7%
Hallucinations	3 (6%)	2 (4%)	66.7%
Anxiety	18 (36%)	4 (8%)	22.2%
Paresthesias	27 (54%)	12 (24%)	44.4%
Pain	27 (54%)	12 (24%)	44.4%
Excessive sweating	16 (32%)	7 (14%)	43.8%
Fatigue	28 (56%)	12 (24%)	42.9%

Discussion

Non-motor fluctuations were found in about half of PD patients. While a recent cohort reported a much lower prevalence of 19%[4], our results are consistent with most published literature[15, 16]. The most common non-motor symptoms with a fluctuating pattern in our population were hallucinations, pain, and paresthesias. Most studies agree that the most common non-motor fluctuations are neuropsychiatric, anxiety is usually more frequently reported, and the prevalence of hallucinations actually ranges from 2-4%[4, 17].

Our findings suggest non-motor fluctuations are independent of motor fluctuations and pharmacological treatment. Once again, the evidence available is inconclusive on this matter. Most authors have proposed that the severity of motor symptoms, assessed with UPDRS Part III, predicts the presence and severity of non-motor fluctuations[16-18]. However, the role of the fluctuating pattern of these motor symptoms in predicting the appearance of non-motor fluctuations is less well established. Similarly, the association of non-motor fluctuations with LEDD, levodopa dose, duration of treatment, and pharmacological classes is conflicting.

These inconsistencies within the available evidence may be due to different study designs, particularly regarding the assessment instruments used. Since there is still no approved scale for the evaluation of non-motor fluctuations, studies have used a wide variety of scores, ranging from empirical interviews[5, 15, 17] to specifically designed questionnaires[19, 20]. Moreover, the populations within these studies significantly differ from one another. For the present study we used the NMSS, which has been previously evaluated to assess non-motor fluctuations[18], as well as the NMFQ, a newly developed instrument that has systematized the empirical interviews applied in the past. We believe this novel approach will help clinicians evaluate non-motor fluctuations more accurately.

The knowledge of the physiopathogenesis of motor fluctuations is still evolving. Most likely they result from a combination of decreased long-duration response to dopaminergic treatment, biochemical variations in the synaptic level of dopamine, and loss of post-synaptic firing tone[21-23]. Since non-dopaminergic neurotransmitters are involved in the development of non-motor symptoms, it is unlikely that the same mechanisms underlying motor fluctuations are responsible for the non-motor ones. Our current findings regarding the lack of association with motor fluctuations support the idea that non-motor fluctuations should obey to more complex processes. Recent studies have suggested that continuous dopaminergic stimulation, either by deep brain stimulation or extended-release medications, improves the severity of non-motor fluctuations[5,24,25]. Whether this effect is related to the known improvement of non-motor symptoms with continuous stimulation, or independent to it, is still unclear.

We acknowledge some limitations to our study. First, the patients included were attending a tertiary referral center, so a referral bias was present with underrepresentation of patients with more severe forms of the disease. Extrapolation of our results to this population should be taken with caution. Second, a relatively small number of patients might underestimate the true prevalence of non-motor fluctuations. However, the heterogeneity of previous studies makes it impossible to calculate an accurate sample size. Finally, the NMFQ has not yet validated for the assessment of non-motor fluctuations. We believe, nonetheless, that the instrument summarizes the most relevant aspects of other scores previously used. Further studies are warrant to confirm these results.

Conclusion

Non-motor fluctuations are frequent. Our findings suggest non-motor fluctuations are independent of motor fluctuations and pharmacological treatment.

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Artículo sin conflicto de interés