

Clinical Study

Nonmotor Symptoms Groups in Parkinson's Disease Patients: Results of a Pilot, Exploratory Study

Santiago Perez Lloret,^{1,2} Malco Rossi,² Marcelo Merello,² Olivier Rascol,¹ and Daniel P. Cardinali^{3,4}

¹ *Department of Clinical Pharmacology and Neurosciences, Faculty of Medicine, Paul Sabatier University, and NSERM CIC9023 and UMR 825 Allées Jules Guesde, 31000 Toulouse, France*

² *Movement Disorders Section, Raul Carrea Institute for Neurological Research (FLENI), Buenos Aires, Argentina*

³ *Departamento de Docencia e Investigación, Facultad de Ciencias Médicas, Pontificia Universidad Católica Argentina, 1107 Buenos Aires, Argentina*

⁴ *Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, 1121 Buenos Aires, Argentina*

Correspondence should be addressed to Santiago Perez Lloret, splloret@fleni.org.ar

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Nonmotor symptoms (NMS) like neuropsychiatric symptoms, sleep disturbances or autonomic symptoms are a common feature of Parkinson's disease (PD). To explore the existence of groups of NMS and to relate them to PD characteristics, 71 idiopathic non-demented PD out-patients were recruited. Sleep was evaluated by the PD Sleep Scale (PDSS). Several neuropsychiatric, gastrointestinal and urogenital symptoms were obtained from the NMSQuest. Sialorrhea or dysphagia severity was obtained from the Unified PD Rating Scale activities of daily living section. MADRS depression scale was also administered. Exploratory factor analysis revealed the presence of 5 factors, explaining 70% of variance. The first factor included PDSS measurement of sleep quality, nocturnal restlessness, off-related problems and daytime somnolence; the second factor included nocturia (PDSS) and nocturnal activity; the third one included gastrointestinal and genitourinary symptoms; the forth one included nocturnal psychosis (PDSS), sialorrhea and dysphagia (UPDRS); and the last one included the MADRS score as well as neuropsychiatric symptoms. Sleep disorders correlated with presence of wearing-off, nocturia with age >69 years, and nocturnal psychosis with levodopa equivalent dose or UPDRS II score. Neuropsychiatric symptoms correlated with UPDRS II+III score and non-tricyclic antidepressants. These results support the occurrence of significant NMS grouping in PD patients.

1. Introduction

Nonmotor symptoms (NMSs) are a frequent feature of Parkinson's disease (PD), affecting up to 60% of patients [1, 2]. These symptoms are usually underrecognized and undertreated, thus leading to a reduced quality of life, to comorbidities, and to precocious institutionalization or hospitalization [2]. Recently, NMS management has been recognized as an important unmet need in PD [3].

NMSs comprise a large variety of symptoms including, among others, neuropsychiatric and sleep disturbances, autonomic dysfunction, and gastrointestinal or sensory symptoms [1, 4]. NMSs can be assessed by several tools

specifically designed for these symptoms, including the NMS questionnaire (NMSQuest) [4], the unified PD rating scale (UPDRS) [5] and the PD sleep scale (PDSS) [6].

Pathophysiologically, NMS may be related to both dopaminergic and nondopaminergic alterations. For example, PET studies reported dopamine dysfunction at the hypothalamus [7]. Degeneration of cholinergic, adrenergic, or serotonergic pathway could also contribute to NMS genesis [8]. Moreover, NMS can precede motor symptoms and thus PD diagnosis [2].

Several studies have suggested that NMS coexist, thus highlighting the possibility of NMS grouping [1, 4, 9]. Identification of such groups can be important for research

on underlying disease mechanisms, since homogeneous groups of patients are more likely to share pathological and genetic features [10]. Therefore, we conducted the present pilot study to explore the existence of NMS groups as well as to relate them to PD characteristics or pharmacological treatment.

2. Methods

2.1. Study Sample. PD patients were recruited from a tertiary outpatient clinic to conduct a study to validate sleep logs use in PD [11]. To be included, the subjects had to fulfill the United Kingdom Parkinson's Disease Society Brain Bank criteria [12]. Patients with minimal state examination (MMSE) score <25 points [13] were excluded.

The protocol conformed the principles enumerated in the Helsinki Declaration and was approved by the Institutional Review Board. All subjects signed an informed consent after full explanation of the procedures.

2.2. PD and NMS Evaluation. PD patients were subjected to cognitive, psychiatric, and motor evaluation including an MMSE [14], a Montgomery-Asberg Depression Rating scale (MADRS) [15], and UPDRS [5]. Medication records were used to calculate levodopa equivalent daily dose (LDED) according to the usual formula [16]. Severities of sialorrhea or dysphagia were obtained from items no. 6 or no. 7 of the UPDRS II (activities of daily living) section.

Presence of sleep disturbances was evaluated by the PDSS [6]. PDSS items were grouped according to domain: sleep quality (items 1 to 3); nocturnal restlessness (items 4 and 5); nocturnal psychosis (items 6 and 7), nocturia (item 8); nocturnal motor symptoms (items 9 to 13) and daytime somnolence (items 14 and 15) (25).

NMSQuest was also administered to patients [1]. Questions were grouped according to the following domains: gastrointestinal motility problems (items 5–7); urinary dysfunction (items 8–9) or neuropsychiatric disorders (i.e., apathy, memory, or attention disorders, items 12–15). Other domains were not included in the analysis.

All participants were instructed to wear an actigraphy device during 7 days (MicroMini-Motionlogger, Ambulatory Monitoring Inc, NY, USA) which served for the calculation of nighttime activity.

2.3. Statistical Analysis. Categorical data were compared using chi-square and numerical variables by an analysis of variance (ANOVA). Exploratory factor analysis (EFA) (with principal components as extraction methods followed by oblique rotation) was first employed to build NMS factors, since between-factor correlations could not be ruled out a priori [17]. The number of factors was determined by inspection of the screen plot and Kaiser's criterion (i.e., eigenvalue >1), and factor scores were calculated. Between-factors correlations were calculated and if all of them were <0.35 (i.e., a determination coefficient ~15%), independency was concluded. In this case, EFA was repeated but employing varimax rotation, which allows better factor definition.

TABLE 1: Patients characteristics.

Males/Females (%)	36 (51)/35 (49)
Age (Mean \pm SD)	68.5 \pm 8.7
UPDRS II+III in ON (Mean \pm SD)	29.1 \pm 14.1
Hoehn&Yahr score	
I	10 (14)
I.5	13 (18)
II/II.5	23 (32)
III	16 (23)
IV/V	9 (13)
PD duration (Mean \pm SD)	7.7 \pm 5.7 years (range: 1–20)
No dopaminergic therapy (%)	15 (21)
Levodopa (%)	45 (63)
Dopamine agonists (%)	42 (60)
LDED (Mean \pm SD)	596 \pm 462
Dyskinesias (%)	34 (47)
Wearing off (%)	35 (49)

LDED: levodopa equivalent daily dose; PD: Parkinson's Disease; SD: standard deviation.

Sampling adequacy was evaluated by Kaiser-Meyer-Olkin (KMO) score, which had to be >0.600. For the evaluation of model validity, communalities were calculated, which had to be >0.50 for all variables. Finally, bivariate and multivariate analyses were employed to disclose the independent variables related to factor scores. For these analyses, factor scores were categorized to their medians. The following independent variables were considered: age, sex, PD duration, UPDRS II total score, UPDRS II+III score, presence of dyskinesias or motor fluctuations (UPDRS IV), administration of levodopa and intake of dopamine agonists, monoamine oxidase inhibitors, catechol-O-methyl transferase inhibitors, antimuscarinics, amantadine, tricyclic or nontricyclic antidepressants, benzodiazepines, and hypnotics.

Bivariate analyses were carried out with chi-square statistic. A multivariate model with factors scores as dependent variables was constructed by forward logistic regression. Only correlates with a significance level in the bivariate analyses were included as explanatory variables in the models. These variables were dichotomized to their medians to help interpretation. Goodness of fit was explored by the Hosmer and Lemeshow score, which was >0.70 in all cases. Potential interactions and multicollinearity were tested for the models, and none was found. All analyses were performed by SPSS v.15 (SPSS Inc. Chicago, Ill).

3. Results

Seventy-one patients were included in this study. A summary of their characteristics is shown in Table 1. EFA revealed the presence of 5 factors with eigenvalues >1 and that explained 70% of variance. KMO score was 0.620. All communalities were >0.50. These results support the validity of the model.

TABLE 2: Results of the exploratory factor analysis.

Items	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Sleep quality (PDSS)	0.789				
Noct. restlessness (PDSS)	0.839				
Off-related problems (PDSS)	0.636				
Daytime somnolence (PDSS)	0.538				
Nocturia (PDSS)		0.839			
Noct. Activity (actigraphy)		0.654			
GU symptoms (NMSQ)			0.935		
GI Motility disorders (NMSQ)			0.939		
Noct. Psychosis (PDSS)				0.572	
Sialorrhea (UPDRS)				0.809	
Dysphagia (UPDRS)				0.668	
MADRS					0.911
NPS symptoms (NMSQ)					0.866
Variance explained by factor	27.6	13.2	11.9	9.8	8.0

GU: genitourinary; GI: gastrointestinal; MADRS: montgomery-Asberg depression Rating scale; NPS: neuropsychiatric symptoms.

Factors loadings are shown in Table 2. The first factor included PDSS measurement of sleep quality, nocturnal restlessness, off-related problems, and daytime somnolence and was thus named “sleep disorders.” The second factor included nocturia (PDSS) and nocturnal activity and was named as “nocturia.” The third one included gastrointestinal and genitourinary symptoms (“autonomic disturbances”). The fourth one comprised nocturnal psychosis (PDSS), sialorrhea, and dysphagia (UPDRS) and was named as “nocturnal psychosis.” The fifth one included MADRS score as well as neuropsychiatric symptoms, being labeled as “neuropsychiatric symptoms.” Only the latter factor score showed some statistically significant correlations with sleep disorders factor score ($r = 0.26$) or with autonomic disturbances factor score ($r = 0.29$). As all correlation coefficients were below 0.35, EFA with varimax rotation was employed, which confirmed the factor structure.

Females showed lower scores for nocturnal psychosis ($F = -0.26 \pm 0.11$, $M = 0.27 \pm 0.20$, $P < .05$) or higher for NPS symptoms ($F = 0.27 \pm 0.17$, $M = -0.27 \pm 0.15$, $P < .05$). Subjects over 69 years old had higher nocturia scores (0.41 ± 0.16 versus -0.39 ± 0.14). Subjects with UPDRS II+III in ON-state >26 had higher scores for NPS symptoms factor (0.34 ± 0.19 versus -0.33 ± 0.12 , $P < .01$). Subjects with UPDRS II in ON-state >9 had higher NPS symptoms factor score (-0.33 ± 0.19 versus 0.32 ± 0.11 , $P < .01$). Subjects with time from PD onset >7 years had higher scores sleep disorders factor (0.26 ± 0.17 versus -0.25 ± 0.15 , $P < .05$), for nocturnal psychosis (0.37 ± 0.19 versus -0.36 ± 0.11 , $P < .05$) or for NPS symptoms (0.25 ± 0.18 versus -0.24 ± 0.15 , $P < .05$). Subjects with wearing-off had higher sleep disorders factor (0.34 ± 0.17 versus -0.31 ± 0.14 , $P < .01$). Subjects with levodopa equivalent dose >625 mg/day had higher scores on sleep disorders (0.21 ± 0.20 versus -0.18 ± 0.10 , $P < .05$) or on nocturnal psychosis (0.36 ± 0.19 versus -0.31 ± 0.19). Subjects on antipsychotics had higher scores on nocturnal psychosis factor (1.16 ± 0.41 versus -0.66 ± 0.12 , $P < .05$). Subjects on nontricyclic antidepressants had

higher scores for NPS symptoms score (0.35 ± 0.14 versus -0.15 ± 0.10 , $P < .05$).

Variables independently related to categorized factor scores were then analysed by logistic regression. Results are shown in Table 3. Sleep disorders correlated with the presence of wearing-off, nocturia with age >69 years, nocturnal psychosis with levodopa equivalent dose, or UPDRS II score, while neuropsychiatric symptoms correlated with UPDRS II+III score, or non-tricyclic antidepressants. Autonomic disturbance symptoms did not show any correlation with other factors.

4. Discussion

The present pilot exploratory study suggests the existence of significant NMS grouping in PD. Such groups, which are usually named “factors” included sleep disorders, nocturia, autonomic disturbance symptoms, nocturnal psychosis, and neuropsychiatric symptoms. These results can contribute to the understanding of NMS underlying mechanism. Indeed, based on the herein reported correlations of NMS with PD characteristics or pharmacological treatments some pathophysiological considerations can be entertained.

Before further discussion, the limitations of the present study must be mentioned. Firstly, the sample size was small, although it included a wide range of subjects and was sufficient to allow sampling adequacy for factor analysis. While grouping of motor symptoms in PD has been extensively explored in the past years [18], to the best of our knowledge, there are no such studies focusing on NMS. Our study, which was conducted in a small precollected database, provides a preliminary impression on the subject, which should be confirmed in larger studies. We believe that they can be useful for generating hypothesis as well as for planning and interpreting future studies.

Secondly, evaluation of NMS was performed only by subjective scales which in some cases have only received partial validation, for example, PDSS or NMSQuest. Moreover,

TABLE 3: Variables independently related to categorized factor scores.

Factor	Independent variables	OR (95% CI)	P value
Sleep disorders	Wearing-off	4.18 (1.54–11.34)	.005
Nocturia	Age >69 years	5.45 (1.96–15.17)	.001
Autonomic disturbances	—	—	—
Nocturnal psychosis	LDED >625 mg/day	3.99 (1.39–11.38)	.01
	UPDRS II >9	2.91 (1.02–8.27)	.045
NPS symptoms	UPDRS II+III >26	4.07 (1.44–11.49)	.008
	Non-tricyclic antidepressants	5.85 (1.08–31.53)	.04

LDED: levodopa equivalent daily dose. 95% CI = 95% confidence interval.

dichotomous variables, such as those produced by the latter, cannot be included in factor analysis as such. Thus, proxy variables depicting numbers of neuropsychiatric, genitourinary, or gastrointestinal symptoms had to be employed, which may not reflect the true nature of these symptoms. In addition, some important and frequent NMS such as orthostatic hypotension, sexual dysfunction, leg swelling, olfactory dysfunction, visual problems, sweating, pain and fatigue, or weight loss could not be included in the analysis because of the aforementioned reason. Moreover, many factors were formed by less than 3 items, which could affect their stability. Future studies should therefore include disaggregated items (i.e., not the number of gastrointestinal symptoms but a measure of the intensity of each one of them). It should be noted that the present study was conducted before NMS development [19]. As this scale can capture frequency and severity of NMS in PD, its use should be important in future NMS grouping studies.

Keeping in mind these limitations, some theoretical hypotheses about the different NMS factors found can be entertained. Subjective complaints of troubled sleep, such as the ones captured by PDSS, have been related mainly to PD severity or depression [6, 10, 20, 21]. In our study, presence of wearing-off was the only variable independently related to troubled sleep factor, which is consistent with previous findings [21, 22]. Progressive neurodegeneration causing loss of long-term response to levodopa would lead to insufficient nighttime dopaminergic tone [23] thus providing a suitable explanation for the findings. In turn, this suggests that nighttime administration of controlled-release levodopa or dopamine agonists or COMT inhibitors could constitute an effective treatment for sleep disorders in PD [24]. Indeed, controlled-release ropinirole has been shown to increase PDSS score [25].

Nocturia has been considered in the past to be related to PD. Our results indicate that this may not be the case and that nocturia is a consequence of normal aging and thus should not be considered within the constellation of NMS in PD. Indeed previous studies did not disclose any difference between PD and healthy controls in this domain [26, 27].

Nocturnal psychosis, as subjectively evaluated by PDSS, was closely related to sialorrhea and dysphagia. It is not the first time that such an odd correlation is reported, and it has been previously related to antipsychotics intake [28]. This appears not to be the case in the present study, as antipsychotics were not statistically related to nocturnal psychosis

in the logistic analysis, while dopaminergic stimulation and disease severity were. It can be possible that increased disease severity is the underlying cause of both oral symptoms and increased dopaminergic stimulation which in turn would lead to psychotic symptoms [29].

Neuropsychiatric symptoms such as depression, apathy, memory, or attention disorders were significantly related to disease severity, in line with previous findings [29]. The detected relationship with non-tricyclic antidepressants can be explained by the fact that they are usually used to treat depression, thus probably revealing a protopathic bias. Finally, gastrointestinal and genitourinary symptoms loaded in the same factor, thus revealing a common origin, probably autonomic dysfunction [30].

In conclusion, EFA found 5 groups of NMS, including troubled sleep, nocturia, gastrointestinal/genitourinary symptoms, sialorrhea/psychotic symptoms, and NPS symptoms, which were related to some PD characteristics. These preliminary findings, resulting from a pilot exploratory study, can be useful for hypothesis generation as well as for planning of future studies.

Conflict of Interests

S. P. Lloret, M. Rossi, M. Merello and D. P. Cardinali have no proprietary, financial, professional, nor any other personal interest of any kind in any product or services and/or company that could be construed or considered to be a potential conflict of interests that might have influenced the views expressed in this paper. O. Rascol has acted as an advisor for most drug companies developing antiparkinsonian medications and has received unrestricted scientific grants from GSK, Novartis, Boehringer-Ingelheim, Faust Pharmaceuticas, Eisai, Lundbeck, TEVA, Euthérapie, and Solvay.

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