

Impact of nonmotor symptoms on disability in patients with Parkinson's disease

Alberto Raggi^a, Matilde Leonardi^a, Francesco Carella^b, Paola Soliveri^b,
Alberto Albanese^{b,c} and Luigi M. Romito^{b,c}

Patients with Parkinson's disease have nonmotor symptoms (NMS) that, although poorly considered, have an impact on their quality of life. In contrast, the effect on disability is not systematically evaluated. Adult patients were consecutively enrolled and administered the Non-Motor Symptoms Questionnaire and the WHO Disability Assessment Schedule. Student's *t*-test was used to assess the difference in the disability score between patients declaring and not declaring NMS. In total, 86 patients were enrolled and reported a median of nine NMS. Patients reporting symptoms in cognitive, emotional, cardiovascular, and sleep functions, as well as those reporting more than nine symptoms as a whole, also reported higher disability levels. The presence of NMS, including little evaluated areas connected to cardiovascular and sleep functions, negatively impacts disability in patients with Parkinson's disease.

Von Morbus Parkinson betroffene Patienten leiden an nichtmotorischen Symptomen, die sich – obgleich unzureichend erfasst – auf die Lebensqualität der Patienten auswirken. Tatsächlich wird der Effekt auf die Behinderung nicht systematisch bewertet. Erwachsene Patienten wurden konsekutiv in eine klinische Studie aufgenommen, in welcher das Non-Motor Symptoms Questionnaire und das World Health Organization Disability Assessment Schedule zur Anwendung kamen. Der Student-*t*-Test wurde zur Beurteilung des Unterschieds im Behinderungs-Score zwischen Patienten verwendet, die angaben, an nichtmotorischen Symptomen zu leiden und denjenigen, die keine nichtmotorischen Symptome mitteilten. In die Studie wurden insgesamt 86 Patienten aufgenommen, die mit einem Medianwert von neun nichtmotorische Symptome angaben. Patienten, die über Symptome wie kognitive, emotionale, kardiovaskuläre und schlafbezogene Funktionsstörungen berichteten, ebenso wie diejenigen, die insgesamt mehr als neun Symptome mitteilten, gaben auch höhere Behinderungsgrade an. Das Vorliegen nichtmotorischer Symptome, einschließlich der unzureichend evaluierten in Bereichen, die mit kardiovaskulären und schlafbezogenen Funktionsstörungen assoziiert sind, wirkt sich bei Patienten mit Morbus Parkinson negativ auf die Behinderung aus.

Las personas que padecen enfermedad de Parkinson sufren de síntomas no motores que, a pesar de ser considerados como menores, ejercen una gran influencia en la calidad de vida de dichos pacientes. Por el contrario,

el efecto que la enfermedad de Parkinson tiene en la discapacidad no se evalúa de forma sistemática. Para realizar este estudio, se entregaron el Cuestionario de síntomas no motores y el Cuestionario de evaluación de la discapacidad de la Organización Mundial de la Salud a una serie de pacientes adultos. Se utilizó la prueba *t* de Student para evaluar las diferencias en la puntuación de discapacidad de los pacientes que habían afirmado padecer o no padecer síntomas no motores. En total, 86 pacientes participaron en el estudio y afirmaron poseer una media de nueve síntomas no motores. También se observaron niveles más elevados de discapacidad en aquellos pacientes que afirmaron poseer síntomas relacionados con las funciones cognitivas, emocionales, cardiovasculares y del sueño, además de los que padecían más de nueve síntomas en total. La presencia de síntomas no motores, así como otros síntomas no evaluados a fondo relacionados con las funciones cardiovasculares y del sueño, ejerce un efecto negativo en los pacientes con enfermedad de Parkinson.

Les patients atteints de la maladie de Parkinson présentent des symptômes non moteurs qui, bien qu'il n'en soit pas toujours tenu compte, ont un impact sur la qualité de vie des patients. Pourtant, l'effet sur le handicap n'est pas systématiquement évalué. Des patients adultes recrutés consécutivement ont répondu au questionnaire sur les symptômes non moteurs et ont suivi le programme d'évaluation du handicap de l'Organisation Mondiale de la Santé. Les tests *t* des étudiants ont été utilisés pour évaluer les différences dans les scores d'invalidité des différents patients déclarant ou ne déclarant pas de symptômes non moteurs. Au total, 86 patients ont été recrutés et ont signalé en moyenne neuf symptômes non moteurs. Les patients signalant des symptômes dans les fonctions cognitives, émotionnelles, cardiovasculaires et du sommeil, ainsi que ceux qui signalaient plus de neuf symptômes en tout, ont également signalé des niveaux d'incapacité plus élevés. La présence de symptômes non moteurs, y compris dans les domaines peu évalués et associés à des fonctions cardio-vasculaires et au sommeil, ont un impact négatif sur l'invalidité chez les patients atteints de la maladie de Parkinson. *International Journal of Rehabilitation Research* 34:316–320 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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^aNeurology, Public Health and Disability Unit – Scientific Directorate,

^bDepartment of Movement Disorders, Neurological Institute C. Besta IRCCS Foundation and ^cUniversità Cattolica del Sacro Cuore, Milan, Italy

Correspondence to Alberto Raggi, PsyD, Neurology, Public Health and Disability Unit – Scientific Directorate, Neurological Institute C. Besta IRCCS Foundation,

Via Celoria 11, 20133 Milan, Italy

Tel: +39 02 2394 3105 x2521; fax: +39 02 2394 2442;

e-mail: araggi@istituto-besta.it

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease whose prevalence, after 60 years of age, varies between 1 and 4% and increases consistently with age, whereas incidence rates vary between 8 and 18/100 000 persons-year (De Lau and Breteler, 2006). PD cardinal motor symptoms are bradykinesia, akinesia, rest tremor, rigidity, and impairment of postural reflexes (Jankovic, 2008) and the relevance of nonmotor symptoms (NMS) is increasingly being recognized (Park and Stacy, 2009; Gallagher *et al.*, 2010). NMS, including mood disturbances, sleep problems, cognition and autonomic disorders, pain, and sexual and urinary problems, have been identified as important symptoms, but remain often undeclared unless specifically investigated (Shulman *et al.*, 2002; Chaudhuri *et al.*, 2010). A reason for this is that there was no reliable instrument to systematically collect these symptoms. However, two instruments are now available for clinical and research purposes: the Non-Motor Symptoms Questionnaire (NMSQuest) (Martinez-Martin *et al.*, 2007), which is a screening tool that can be used to report NMS that could otherwise remain undeclared and the Non-Motor Symptoms Scale (Chaudhuri *et al.*, 2007), which is an evaluation tool that can be used to assess the severity and frequency of NMS.

Among NMS, depression, dementia, psychosis, cognitive impairment, apathy, and sleep disorders (e.g. urinary incontinence, restlessness, morning fatigue, and somnolence) were found to be the most common and relevant determinants of reduced health-related quality of life (HRQoL) and increased disability (Muslimovic *et al.*, 2008; Gomez-Esteban *et al.*, 2011; Post *et al.*, 2011; Winter *et al.*, 2011). The specific impact of NMS on HRQoL has been evaluated in a recent study (Martinez-Martin *et al.*, 2011) which demonstrated a close association between the number, frequency, and severity of NMS and reduced HRQoL. However, the specific impact of NMS on disability has not been systematically evaluated as yet. In contrast, there is a huge amount of literature addressing the role of motor symptoms, such as axial impairment, dyskinesias, freezing of gait, reduced lower extremity strength, and motor fluctuations, as factors influencing disability and HRQoL in patients with PD (Gomez-Esteban *et al.*, 2007; Muslimovic *et al.*, 2008; Duncan and Earhart, 2011; Post *et al.*, 2011; Winter *et al.*, 2011).

Disability is conceptualized by WHO's International Classification of Functioning (ICF), Disability and Health as the negative interaction between an individual

with a health condition and the factors existing in the context in which the individual lives (World Health Organization, 2001): this interaction is observable in terms of activity limitation and restriction to participation. The aim of this study is to evaluate the impact of NMS on disability in patients with PD, intended as a limitation in performing activities due to a health condition.

Methods

Study design, patients, and assessments

The study design was cross-sectional. Patients were consecutively enrolled at the division of Neurology I – Movement Disorders of the Neurological Institute C. Besta IRCCS Foundation of Milan. The inclusion criteria were diagnosis of PD according to the UK Parkinson's Disease Brain Bank criteria (Hughes *et al.*, 1992) and age greater than 18. The exclusion criteria were eligibility for technological PD treatment, the presence of psychiatric comorbidities, or inability to participate in a structured interview. Patients enrolled in clinical trials in the previous three years were also excluded.

The study was approved by the Institute's ethical committee and patients gave their written consent to participate: those unable or unwilling to provide informed consent were excluded.

Hoehn and Yahr (HY) staging (Hoehn and Yahr, 1967) was used to assess the clinical aspects of PD. The prevalence of NMS was evaluated using the NMSQuest (Martinez-Martin *et al.*, 2007), a 30-item screening tool composed of nine subscales (Digestive, Urinary, Attention and Memory, Hallucinations/Delusions, Depression/Anxiety, Sexual, Cardiovascular, Sleep, Miscellany). Respondents have to mark each item in case they experienced the symptom described during the previous month: therefore, the NMSQuest reports information about the prevalence of NMS, but not about severity. Subscales and a general score, which ranges between 0 and 30, are available: higher scores indicate the presence of more NMS.

Disability was measured with the WHO-Disability Assessment Schedule (WHO-DAS II), a 36-item ICF-based tool that examines the difficulties experienced in undertaking several activities in the previous month due to a health condition (Üstün *et al.*, 2010). For each item, respondents have to report how much difficulty they experienced in performing the task on a 1–5 scale (from 'no difficulty' to 'complete difficulty/cannot do the activity'): therefore, the WHO-DAS II reports information about the intensity of problems in performing an

activity. Both a total score and six subscores are available: Understanding and communicating; Getting around; Self-care; Getting along with people; Life activities (divided into household and work) and Participation in society. Scores range from 0 to 100, with higher scores reflecting greater disability.

The NMSQuest and the WHO-DAS II were administered by researchers who were specifically trained for their utilization (Francescutti *et al.*, 2009).

Data analysis

Descriptive statistics were used as needed to report on demographic and clinical issues. To assess the impact of NMS on disability, each domain of NMSQuest was broken down into two groups: the first composed of patients reporting no symptoms and the other of patients reporting at least one symptom. A second grouping variable was the NMSQuest total score: patients were divided into two groups, namely those who reported less than the median number of NMS and those who reported a higher or equal number of symptoms.

The one-sample Kolmogorov-Smirnov test confirmed that the WHO-DAS II summary scores were normally distributed; therefore, differences between patients with and without NMS were assessed using Student's *t*-test. Statistical significance was set at $P < 0.05$.

Results

In total, 86 patients (55 men, mean age 63.9, SD 11.6) were included in the data analysis. They were mostly married (60) and not employed (67); 11 were in HY stage I, 50 in stage II, 22 in stage III, and three in stage IV.

The prevalence of NMS is reported in Table 1: the range of symptoms varied between 1 and 29 (median 9, interquartile range 6–13). Differences in the WHO-DAS II summary score between patients reporting and not reporting NMS are presented in Table 2. Patients declaring at least one symptom reported higher WHO-DAS II scores and the difference was significant when symptoms related to attention and memory, emotional functions, cardiovascular, and sleep disturbances were taken into account. When the total NMSQuest score was taken into account, those reporting less than nine symptoms had significantly lower WHO-DAS II scores than those reporting a number of symptoms higher than or equal to nine.

Discussion

The results of this study show that patients declaring at least one symptom in domains related to attention and memory, emotional functions, cardiovascular, and sleep functions report significantly higher disability levels than those without symptoms. Similarly, patients who declared a number of NMS higher than nine among the entire set of NMSQuest items also reported higher disability levels.

Table 1 Prevalence of nonmotor symptoms

Item	Percentage of patients reporting symptom
Nocturia	61.5
Sad, blues	57.3
Constipation	43.8
Urgency	51.0
Acting out during dreams	43.8
Anxiety	49.0
Sex – difficulty	42.7
Insomnia	49.0
Restless legs	41.7
Dribbling of saliva	40.6
Remembering	39.6
Dizzy	39.6
Bowel emptying incomplete	38.5
Pains	35.4
Loss of interest	35.4
Sex – drive	35.4
Concentration	31.3
Swallowing	22.9
Intense, vivid dreams	22.9
Swelling	29.2
Sweating	27.1
Vomiting	19.8
Weight	25.0
Taste/smelling	24.0
Daytime sleepiness	17.7
Diplopia	17.7
Falling	14.6
Hallucinations	11.5
Bowel incontinence	6.3
Delusions	2.1

Therefore, our results account for a preliminary indication of the impact on NMS on increased disability.

The effects of NMS on disability have been evaluated in few previous studies that used scales II and III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn *et al.*, 1987) describing activities of daily living (ADL) and motor impairments, therefore obtaining a partial picture of the disability associated with PD or evaluating a restricted number of NMS. Pankratz *et al.* (2008) demonstrated that depressive symptoms were correlated to the stage of illness, motor impairment, and functional disability. Weintraub *et al.* (2004) showed that NMS, specifically depression and cognitive impairment, contribute significantly to disability, measured using the UPDRS scale of ADL in patients with PD. Witjas *et al.* (2002) reported that the presence of nonmotor fluctuations related to dysautonomic, mental, and sensory functions was associated with increased disability. However, disability was self-reported by respondents on a five-step scale from 0 (no disability) to 4 (maximum discomfort), which represented a nonreliable measure of what kind of difficulty patients experienced.

The results of our study confirm previously reported ones and also expand them by adding new insights on the impact of NMS related to cardiovascular and sleep disturbances, to that of known NMS such as those related to cognitive and emotional functions. The difference was even stronger when patients reporting less than nine symptoms were compared with those

Table 2 Differences in the WHO-DAS II summary score in patients with and without nonmotor symptoms

NMSQuest domains	Patients' group (n)	WHO-DAS II summary score (mean $\pm$ SD)	t-test
Digestive	With symptoms (71)	20.3 $\pm$ 14.8	1.43
	Without symptoms (14)	14.2 $\pm$ 11.5	
Urinary	With symptoms (63)	20.8 $\pm$ 15.5	1.99
	Without symptoms (23)	15.2 $\pm$ 9.8	
Attention/memory	With symptoms (49)	23.9 $\pm$ 15.4	3.91**
	Without symptoms (37)	13.2 $\pm$ 10.1	
Hallucinations/delusions	With symptoms (10)	20.9 $\pm$ 21.3	1.58
	Without symptoms (76)	18.0 $\pm$ 12.9	
Depression/anxiety	With symptoms (60)	22.1 $\pm$ 15.4	3.42**
	Without symptoms (26)	12.9 $\pm$ 9.1	
Sexual functions	With symptoms (42)	20.6 $\pm$ 16.3	1.72
	Without symptoms (33)	15.4 $\pm$ 9.3	
Cardiovascular	With symptoms (40)	23.6 $\pm$ 15.3	2.70**
	Without symptoms (46)	15.5 $\pm$ 12.4	
Sleep disorders	With symptoms (71)	21.0 $\pm$ 14.7	2.52*
	Without symptoms (15)	11.1 $\pm$ 9.1	
Miscellany	With symptoms (63)	20.3 $\pm$ 14.2	1.06
	Without symptoms (23)	16.6 $\pm$ 14.6	
NMSQuest total score	NMSQuest $\geq$ 9 (47)	25.8 $\pm$ 14.0	5.54**
	NMSQuest < 9 (39)	11.5 $\pm$ 8.6	

NMSQuest, Non-Motor Symptoms Questionnaire; WHO-DAS II, WHO-Disability Assessment Schedule.

*Student's *t*-test significant at $P < 0.05$.

**Student's *t*-test significant at $P < 0.01$.

reporting nine or more symptoms, independent of the kind of symptoms. The added value of this study lies in the utilization of the WHO-DAS II that measures disability not only on a restricted set of difficulties linked to mobility and ADL but also with items related to communication, relationships, and participation in social activities. At the same time, it cannot be ignored that the contents of some NMSQuest and WHO-DAS II items, if not similar, are connected to each other. This is the case, for example, of NMSQuest items related to attention and memory and WHO-DAS II items related to understanding and communicating, or those related to cardiovascular symptoms with those related to mobility. Although the NMSQuest refers to symptoms and the WHO-DAS II refers to activities, it is likely that these items are strongly interconnected.

These domains of functioning were evaluated for their sensitivity to clinical severity in a wide set of patients, including those with PD, from clinical settings in a recent paper from Garin *et al.* (2010): the results accounted for significant differences for the vast majority of domains and health conditions. For the purpose of Garin's study, PD severity was evaluated with the HY score: patients in stage I were assigned to the mild group, those in stage II to the moderate group, and those in stage III or higher to the severe group. Significant differences were observed in the majority of WHO-DAS II scores among patients in the mild and severe groups. The WHO-DAS II is a reliable and valid outcome measure that, due to its multiaxial composition, may be useful in the evaluation of

disability in patients with PD, to evaluate the impact of both motor symptoms, as already shown, and NMS. Disability in patients with PD cannot be in fact only described in terms of motor-related problems, but rather it should be conceptualized in terms of body impairments and difficulties in activities and participation. Although mobility-related functions and activities are of primary relevance, the presence of problems related to urination, sleep, pain, and emotional functions was previously reported in a percentage between 53 and 77% of patients (Raggi *et al.*, 2011). The results of the present study reinforce previous findings by showing the specific impact of NMS on the understanding of disability in patients with PD. However, it should be noted that the conceptualization of disability in this paper only partially reflects that of the ICF classification. In particular, what we addressed is the degree to which patients with a higher number of NMS report the amount of activity limitations, thus not intending a causal relationship. The main reason for this is that a causal relationship, strictly referring to an ICF-based model of disability, would be hardly definable as persons' functional profiles are highly based on the context in which the individuals live. An ICF-based model is, in fact, much more focused on the process by which decrements in functioning arise as a consequence of a combined effect of problems with body functions and structures and of problems in the physical and attitudinal environment (Üstün *et al.*, 2003).

Some limitations need to be taken into account. The first limitation lies in the cross-sectional design, which does

not enable definition of causal relationships. In this regard, it should, however, be noted that the identification of causal relationships is not within the scope of the paper. The second limitation is the sample, which included a limited number of patients attending to a specialized center, and majority of the enrolled patients were in HY stage I or II, limiting the possibility to generalize results to the entire PD patient population.

Considering these limitations, we can conclude that our study provides a preliminary indication of the impact of NMS on disability in patients with PD: those with nine or more NMS reported higher disability. In particular, the effect of cardiovascular and sleep disturbances, in addition to known symptoms related to cognitive and emotional functions, was reported as relevant.

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Conflicts of interest

There are no conflicts of interest.

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