Neuropsychiatric disorders in patients with mild cognitive impairment and dementia associated with Parkinson's disease

Nilton Custodio[1-3], Sheila Castro-Suarez[4], Eder Herrera-Pérez[1,5], David Lira[1-3], Rosa Montesinos[1,6], Erik Guevara-Silva[7], Liza Núñez del Prado[8], Nora Rojas[8].

ABSTRACT

Neuropsychiatric symptoms (NPS) are common in Parkinson's disease (PD), regardless of the cognitive state of patients, but they are more frequent and severe in later stages of this disease. **Objectives:** to know the frequency and type of NPS, by applying a global measurement scale in PD patients. **Patients and methods:** Three groups were prospectively formed: 22 patients diagnosed with PD and normal cognition (PD-CN), 18 patients with mild cognitive impairment associated with PD (PD-MCI), and 23 patients with dementia associated with PD (PDD). Following an ordered protocol, these individuals were subjected to successive examinations of screening, diagnosis, and type of cognitive impairment, and then they were examined with the Neuropsychiatric Inventory (NPI). **Results:** The most common symptoms in patients with PD–CN and PD-MCI were: depression (68.1% and 66.6% respectively), anxiety (63.6% and 66.6% respectively), and apathy (45.5% and 55.5% respectively); while in patients with PDD, the most common symptoms were: anxiety (60.9%), sleep disorders (52.2%), and apathy (47.8%). **Conclusions:** Depression, apathy, and anxiety are the three most commonly reported symptoms in patients with PD-CN, PD-MCI, and PDD; with prevalence for each symptom of approximately 50% out of all the cases (except for depression in PDD, present in less than half of the patients). Our study draws attention to analyze the full spectrum of PD behavioral characteristics from early stages.

Key words: Cognition. Dementia. Parkinson's disease. Neuropsychiatric symptom.

1. Unidad de Diagnóstico de Deterioro Cognitivo y Prevención de Demencia. Clínica Internacional. Lima, Perú.
2. Unidad de Investigación. Clínica Internacional. Lima, Perú.
3. Servicio de Neurología. Clínica Internacional. Lima, Perú.
4. Servicio de Neurología de la Conducta. Instituto Nacional de Ciencias Neurológicas. Lima, Perú.
5. Unidad de Proyectos de Investigación. Instituto de Salud del Niño. Lima, Perú.
6. Servicio de Medicina de Rehabilitación. Clínica Internacional. Lima, Perú.
7. Departamento de Medicina. Hospital San Juan de Lurigancho. Lima, Perú.
8. Servicio de Neurología. Clínica Maison de Santé. Lima, Perú.

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms such as bradykinesia, rigidity, postural instability, and tremor; but it also presents non-motor symptoms, including impairments of sensorial, autonomous, cognitive, and behavioral functions, as well as functions of sleep[1]. It has been stated that clinical spectrum of cognitive impairments in PD patients seems to be a continuum which may range from the slight involvement restricted to specific cognitive domains, mild cognitive impairment (MCI) without dementia (PD-MCI), to real dementia in final stages (PDD)[2]. In this regard, a high percentage of patients will develop neuropsychiatric symptoms (NPS)[3,4] — regardless of the involvement of cognitive functions – which will contribute to decrease their quality of life, and to increase responsibility for their caregivers. Depression is frequent; it can reach up to 40% of prevalence, and may include apathy, anxiety, low motivation and/or non-specific motor complaints[5]. It is not clear whether depression is reactive to PD diagnosis, movement limitations, loss of independence, or whether it is a different clinical condition –result of dopaminergic and/or non-dopaminergic neuro-degeneration occurring in PD [6]—. Psychotic symptoms can reach prevalence of 21 to 46%, and may be as mild (vivid dreams, visual illusions and ideas of presence) as severe (paranoid ideas, visual hallucinations, auditory hallucinations, false identifications)[7]. Hallucinations are four times more common in individuals with PDD than in patients with PD without dementia. Phenomenologically, psychotic symptoms of PDD are indistinguishable from dementia with Lewy bodies, but their incidence is much higher in the latter[7,8]. Hallucinations are mostly visual, and may also be auditory or tactile, in which case, they usually coexist with the first ones. Hallucinations commonly involve people or animals, and may or may not, disturb the patient[3]. Delusions may involve the belief of sexual infidelity by the spouse, and it use to be very stressful for both the patient and the caregiver. On the other hand, NPS may also be triggered by changes in the treatment of motor symptoms with antiparkinsonian drugs, although the cause and effect relationship has not been established yet. Indeed, changes of levodopa plasma levels (peak-dose) do not appear to be a direct trigger[9]. In this regard, Catechol-O-methyltransferase inhibitors, which extend the length of levodopa action, are the least likely to make psychotic symptoms worse, compared to other antiparkinsonian drugs. Many studies of dopamine agonists report adverse effects such as hallucinations, but there are no direct comparisons of agonists to assess whether these apparent differences are significant[10,11]. In order to know the frequency and type of NPS, as well as the results of applying a global measurement scale in patients with PD-CN, PD-MCI and PDD, we propose this research study in the Unit of diagnosis of Cognitive Impairment and Dementia Prevention of the *Clínica Internacional*.

PATIENTS AND METHODS

Participants: a descriptive comparative study was designed, which included 63 individuals openly selected, and who went to the Unit of diagnosis of Cognitive Impairment and Dementia Prevention of the *Clínica Internacional*, between January 2008 and December 2012. The following groups were studied: 22 individuals diagnosed with PD-CN, 18 with PD-MCI, and 23 with PDD, depending on severity of dementia symptoms, based on the scale Clinical Dementia Rating (CDR)[12]. Inclusion criteria for this study were: individuals of both genders, people older than 50 years old, people diagnosed with PD according to the clinical criteria of the United Kingdom Parkinson's disease Society Brain Bank[13]; PD stage was established according to the Hoehn-Yahr scale[14]; and for patients diagnosed with dementia we used the criteria of the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[15], starting cognitive symptoms at least one year after of being diagnosed with PD. Patients were treated according to the criteria of neurologists of the study, with levodopa and/or pramipexole, for managing motor symptoms; and neuroleptics, antidepressants and/or benzodiazepines for NPS. Exclusion criteria were: individuals with difficulty to take cognitive tests due to auditory, visual or any other physical problems, which might interfere in their performance; non-Spanish speaking individuals with low level of education (defined as those with less than four years of schooling), those scored more than 4 in the criteria of the index modified

by Hachinski, those with concomitant cerebrovascular pathology, history of addiction or substance abuse, and individuals with cognitive impairment explained by other causes, such as hypothyroidism, deficiency of vitamin B-12, hepatopathy, chronic nephropathy, neuro-infections (infection related to HIV, syphilis), severe cranioencephalic trauma, subdural hematoma, among others.

All participants and their caregivers (depending on the case) signed an informed consent form, in accordance with ethical guidelines for researches on human beings. The study protocol was approved by the Research Unit of the *Clínica Internacional* and the Ethics Committee of the *Universidad San Martín de Porres*.

Clinical and neuropsychological assessment: individuals diagnosed with PD were subjected to successive examinations of screening, diagnosis of dementia and type of dementia. During screening phase, individuals had an integrated clinical assessment and took brief cognitive tests, including: Mini Mental State Examination (MMSE)[16], clock drawing test – Hands version (CDT-M)[17] and Pfeffer Functional Activities Questionnaire (PFAQ)[18]. Individuals scored below the established for this research protocol, at least in one of the screening tests, were subjected to a second assessment, where a second MMSE and CDT-M was applied by an evaluator other than that one who did the screening phase. The cut-off point in MMSE, for suspicion of dementia, was adjusted according to years of schooling: 27 for individuals with more than 7 years of schooling, 23 for those with 4 to 7 years of schooling, 22 for those with 1 to 3 years of schooling, and 18 for illiterates. The CDT-M assesses individual's capacity to put on a drawn circle, the numbers from 1 to 12, just the way a clock is, and then it evaluates direction and proportionality of clock hands when trying to capture 11:10 hours. Maximum score is 10, and for Peruvian people the score lower than 7 implies cognitive involvement [17]. The PFAQ includes 11 questions about activities of daily life, with scores ranging from 0 to 3 according to severity of disability for each activity. Maximum score is 33, and a score higher than 5 shows functional involvement[18]. Individuals who confirmed cognitive impairment in the second tests were subjected to blood tests such as levels of hemoglobin, glucose, urea, creatinine, liver function tests (TGO and TGP), albumin and globulin serum levels, vitamin B12 and folic acid dosage, screening test for syphilis (VDRL), screening test for HIV (HIV Elisa), thyroid profile (T3, T4, and TSH), serum electrolyte levels (sodium, potassium and chloride), as well as brain scan and/or magnetic resonance imaging, assessment of depressive symptoms (Beck Depression Inventory, BDI-II) for screening cognitive impairment related to depression, and the Peruvian adaptation of the Addenbroke's Cognitive examination (ACE)[19] and the scale CDR12 were applied. In the last phase, and with the results of hematological tests, brain images, and neuropsychological report, a diagnosis according to the type of dementia was made, by consensus among neurologists and neuropsychologists of the team. Patients with normal screening results were assessed with a standard neuropsychological test, in order to separate patients with PD-CN from patients with PD-MCI. Neuropsychological set consisted of the following tests: Logical Memory Subtest from the Weschler Memory Scale reviewed for verbal memory, and the Rey Complex Figure test for visual-space memory. For executive functions, we evaluated categorization with the Wisconsin Card Sorting Test (WCST), digits forwards for the span of attention, Trail Making Test (TMT) A and B for alternate attention, color and word test by Stroop for inhibition, digits backwards for work memory and verbal fluency for planning verbal material. To evaluate language, we used semantic fluency and the Boston Naming Test; while for visual-perception abilities we used copies of drawing by Strub and Black, and cube test of the WAIS-III. Neuropsychological set consisted of the Neuropsychiatric Inventory20 (NPI) of 12 items. In the cases of the color and words test by Stroop and the TMT A and B, values were adjusted to minimize a possible effect of motor slowing-down in the PD patient.

Data analysis: Patients diagnosed with PD were divided in three groups according to the clinical, neurological and neuropsychological assessment:

Cognitively normal patients with Parkinson's disease (PD-CN): they were patients diagnosed with PD and normal neuropsychological assessment.

Patients with mild cognitive impairment associated with Parkinson's disease (PD-MCI): patients with PD and non-specific cognitive complaints referred by the patient or his relatives, or a report of some relative declination

in the cognitive function during the last year—whether by the patient or a caregiver, and confirmed by the neuropsychological assessment –without dementia and changes in activities of daily life.

Patients with dementia associated with Parkinson's disease (PDD): include patients with PD and dementia, according to the criteria of DSM-IV, whose dementia began one year after the beginning of PD motor symptoms and without features of dementia with Lewy bodies.

NPS were assessed with the NPI20, and include 12 symptoms: delusions, hallucinations, agitation/aggressiveness, depression/dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep rhythm changes, and appetite changes. The presence or absence of each NPS was evaluated giving value 1 to the presence of one symptom and ‹0› to its absence. Then, symptoms were assessed both in severity (range from 0 to 3), and frequency (range from 0 to 4). Finally, a score of intensity was estimated when multiplying scores of severity and frequency (range from 0 to 12 for each NPS). The total score of NPI was obtained adding the 12 scores of intensity (range from 0 to 144).

Demographic variables were compared among the three groups using the one-way variance analysis (ANOVA) with Bonferroni post hoc comparisons when necessary. For those categorical variables (e.g., gender), the percentages were compared using the Chi-square test. To evaluate NPS, we used measures of central tendency, through the average score for each individual item of all patients, of those patients who showed at least some NPS, and the percentage of those who were scored more than or equal to 4 in each item of the NPI.

RESULTS

In this sample of PD patients we found no statistically significant differences in age, gender, years of education, duration of PD in years, and performance in Depression Inventory (Test T, $p = 0.55$; $p = 0.43$; $p = 0.58$; $p = 0.08$; $p = 0.17$; respectively), although there is a slight tendency towards more years of disease in PDD patients. The ACE performance in PD-MCI ($p < 0.001$) and PDD ($p < 0.001$) is significantly lower compared to the group of PD-CN patients. Although there is a tendency in the best performance of the ACE favoring the PD-CN group, regarding the PD-MCI group, this does not reach statistically significant difference ($p = 0.09$). Likewise, the PD-MCI group performs better in ACE when compared to the PDD group ($p < 0.001$) (see Table 1). The average length of PD diagnosis in the group of PDD patients was years, with the bottom quartile in four years and the top quartile in twelve years. Only one patient from the PDD group were in stage I of Hoehn-Yahr, while eight patients were in stage II, eleven patients in stage III, and three patients in stage IV. Regardless of cognitive status, levodopa (in an average daily dose of 573.5 ± 261.6 mg) was used in 85.5% of patients in this sample, while the dopaminergic agonist (pramipexole) was used in 27.6%, neuroleptics in 19.8 %, antidepressants in 8.5%, and benzodiazepines in 24.8% of the total sample of PD patients.

Table 1. Demographic characteristics of patients with Parkinson's disease according to the cognitive impairment level (PD-CN, PD-MCI and PDD).

	PD-CN n = 22	PD-MCI n = 18	PDD N = 23	P
Age	63.9 (6.3)	70.6 (8.2)	71.4 (7.1)	NS
Gender (F:M)	7:15	7:11	8:15	NS
Education (in years)	10.9 (2.5)	10.1 (2.4)	10.3 (2.6)	NS
PD Duration (in years)	6.2 (3.4)	6.4 (2.7)	8.8 (5.9)	NS
Hoehn-Yahr	1.8 (0,6)	2.1 (0.4)	2.6 (0.3)	< 0.01*
BDI-II	12.3 (2.7)	11.5 (4.3)	12.2 (6.7)	NS
ACE	91.9 (3.3)	84.3 (4.1)	74.9 (4.6)	< 0.001*†

* PD-CN vs. PDD $p < 0.01$ †PD-MCI vs. PDD $p < 0.01$

BDI-II: Beck Depression Inventory–version II. MMSE: Mini Mental State Examination. ACE: Addenbroke's Cognitive Examination. Results in parentheses correspond to standard deviation (SD).

Table 2. Average score of the items in the Neuropsychiatric Inventory (NPI) in all patients with Parkinson's disease, according to cognitive impairment level and patients showing symptoms.

Item NPI	PD-CN (n = 22)			PD-MCI (n = 18)			PDD (n = 23)		
	All	Patients con NPS		All	Patients con NPS		All	Pacientes con SNP	
	Points in NPI mean (SD)	Points in NPI mean (SD)	Percentage with NPI ≥4 N (% total)	Points in NPI mean (SD)	Points in NPI mean (SD)	Percentage with NPI ≥4 N (% total)	Points in NPI mean (SD)	Points in NPI mean (SD)	Percentage with NPI ≥4 N (% total)
Delusions	0.43 (1.38)	3.36 (2.79)	2 (9.1)	1.25 (1.27)	2.45 (2.13)	4 (22.2)	1.98 (3.56)	4.96 (3.74)	6 (26.1)
Hallucinations	0.48 (1.53)	2.90 (2.38)	2 (9.1)	0.87 (1.45)	2.06 (1.98)	3 (16.6)	1,99 (3.12)	3.93 (3.42)	5 (21.7)
Agitation / aggressiveness	0.58 (1.52)	2.54 (227)	1 (4.5)	0.67 (1.58)	2.24 (2.18)	4 (22.2)	1.31 (2.23)	2.98 (2.48)	3 (13)
Depression / dysphoria	2.37 (2.65)	3.46 (2.63)	7 (31.8)	2.59 (2.08)	2.17 (2.34)	3 (16.6)	1.56 (2.56)	3.16 (2.88)	4 (17.4)
Anxiety	2.23 (2.49)	3.25 (2.56)	6 (27.3)	2.81 (2.12)	3.96 (2.71)	6 (33.3)	1.83 (2.71)	3.17 (2.79)	5 (21.7)
Euphoria	0.24 (1.11)	2.25 (2.38)	1 (4.5)	0.28 (1.23)	2.23 (2.16)	3 (16.6)	0.18 (0.68)	1.51 (1.1)	1 (4.3)
Apathy	1.41 (2.10)	2.91 (2.49)	4 (18.2)	1.98 (1.89)	3.56 (2.54)	7 (38.9)	2.58 (3.59)	4.77 (3.49)	8 (34.8)
Disinhibition	0.25 (0.93)	2.12 (1.98)	2 (9.1)	0.57 (1.12)	2.28 (1.76)	3 (16.6)	0.46 (1.23)	2.46 (2.1)	1 (4.3)
Irritability	1.12 (1.79)	2,42 (1.12)	4 (18.2)	1.25 (1.68)	3.81 (2.37)	5 (27.8)	1.42 (2.47)	3.53 (2.96)	3 (13)
Aberrant motor behavior	0.28 (1.27)	2.78 (2.48)	1 (4.5)	0.75 (1.43)	2.16 (1.76)	3 (16.6)	1.32 (2.48)	3.56 (3.8)	4 (17.4)
Sleep disorders	1.34 (0.98)	3.16 (2.45)	2 (9.1)	1.45 (1.16)	3.16 (1.76)	6 (33.3)	2.56 (3.67)	4.87 (3.71)	8 (34.8)
Appetite problems	0.47 (0.36)	2.56 (1.89)	2 (9.1)	1.21 (0.76)	2.68 (1.94)	4 (22.2)	1.97 (3.84)	4.14 (3.88)	6 (26.1)
NPI TOTAL	**9.64 (9.36)**	**11.24 (10.43)**	**14 (63.6)**	**12.13 (10.76)**	**14.35 (11.56)**	**13 (72.2)**	**19.35 (20.43)**	**21.42 (20.54)**	**17 (73.9)**

Table 2 shows the average score for each individual item of all the PD-CN patients, of those patients who showed at least some NPS (n = 18; 81.8%) and the percentage of those who obtained a score higher than or equal to 4 in each item of the NPI (63.6%). The average score and standard deviation (SD) of the NPI of all patients in the PD-CN group was 9.64 ± 9.36, respectively. The most common symptoms were depression (n = 15; 68.1%) and anxiety (n = 14; 63.6%), followed by apathy (n = 10; 45.5%) and irritability (n = 9; 40.9%). 77.7% of those who had at least one NPS (representing 63.6% out of the total group) had at least one symptom with a score higher than or equal to 4. Among these patients, the highest score corresponded to depression (3.46 ± 2.63) and delusions (3.36 ± 2.79), followed by anxiety (3.25 ± 2.56) and apathy (2.91 ± 2.49).

In PD-MCI the percentage of patients who had at least one NPS was 83.3% (15 individuals), while that of patients reaching a score higher than or equal to 4 for at least one item of the NPI was 72.2%. The average score and standard deviation of the NPI for all the PD-MCI patients was 12.13 ± 10.76, respectively. The most common symptoms were anxiety (n = 12; 66.6%), depression (n = 12; 66.6%) and apathy (n = 10; 55.5%). Among patients who had at least one NPS and one symptom scored higher than or equal to 4, the highest scores were obtained in the items of anxiety (3.96 ± 2.71), apathy (3.56 ± 2.54), irritability (3.21 ± 2.37) and sleep disorders (3.16 ± 1.76).

Most patients of the PDD group (n = 21; 91.3%) had at least one NPS, while the percentage of patients

Table 3. Percentage of patients with NPS out of PDD patients.

Neuropsychiatric Symptoms	N	%
Delusions	5	21.7
Hallucinations	8	34.7
Agitation / aggressiveness	10	43.5
Depression / dysphoria	4	17.4
Anxiety	14	60.9
Euphoria	3	13.0
Apathy	11	47.8
Disinhibition	4	17.4
Irritability	9	39.1
Aberrant motor behavior	8	34.7
Sleep disorders	12	52.2
Appetite problems	8	34.7

reaching a score higher than or equal to 4 at least in one item of the NPI was 73.9%. The average score and standard deviation of the NPI for all patients of the PDD group was 19.35 ± 20.43 (DS). The most common symptoms were anxiety (n = 14; 60.9%), sleep disorders (n = 12; 52.2%), and apathy (n = 11; 47.8%), while the least common were: euphoria (n = 3; 13.0%), and disinhibition (n = 4; 17.4%) (see Table 3). Among patients with NPS and at least one symptom scored 4 or more, the highest scores were obtained for the items of delusions (4.96 ± 3.74), apathy (4.77 ± 3.49), sleep disorders (4.87 ± 3.71), and appetite problems (4.14 ± 3.28).

DISCUSSION

In spite of being a cross-sectional study, our research reflects previous findings on frequency and type of NPS in PD patients, where we have demonstrated the high prevalence of such symptoms –both in PD-CN patients[21,22] and PDD patients[3,4] – suggesting their existence and greater severity in PDD is primarily associated with disease progression[21]. In PD-CN patients, the frequency of some NPS was 81.8%, with a moderate impairment in 63.6%; lower than that found in a study by Kulisevsky, University of Barcelona (87% and 65% respectively)[21], and by Aarsland, University of Stavanger (89% of patients had at least one NPS)[23], but higher than that found in the study based on population in the Cache County Study[24]. In this group of patients, depression and anxiety were the most commonly reported symptoms, affecting almost 70% of patients, and apathy was present in approximately one of every two patients. Likewise, depression (3.46 ± 2.63), anxiety (3.25 ± 2.56), and delusions (3.36 ± 2.79) were the most severe symptoms. However, these symptoms showed low prevalence and severity –as reflected in the total score of the NPI which is three times higher (2.96 vs. 9.64) –similar findings to those ones previously reported[21], but higher than those reported by Aarsland et at3, where the accurate prevalence of some NPS (61%) and the average score of the NPI (7.1 ± 10) were much lower than those ones found in our study. These differences can not be explained by the clinical or demographic characteristics of both studies, but the use of concomitant neuroleptic medication could be an alternative. In the same way, the percentage of patients with at least one NPS, and the average score of the NPI for the group of PD-MCI patients were 83.3% and 12.13 points, respectively; and in the case of PDD were 91.3% and 19.35 points, being higher. We found no significant differences between the percentages of the most common NPS between both groups, but a tendency where apathy may be more frequent in patients with PD-MCI is observed.

In the group of our PDD patients, most of them (91.3%) had at least one NPS, being the most common: anxiety, sleep disorders, and apathy; findings which are similar to those reported by Lee[25] and Emre[26]. However, the frequency of certain NPS in our series of PDD patients was similar to the series by Lee[25]; this was higher than that reported by Aarsland[23] in items such as hallucinations (34.7% vs. 24.6%), agitation (43.5% vs. 32.6%), irritability (39.1% vs. 29.7%), and aberrant motor behavior (34.7% vs. 22%). Similar to the findings by Lee[25] and Kulisevsky[21], we found high prevalence of certain items of the NPI in PDD patients compared to PD-CN, regarding to sleep disorders (52.2% vs. 22.7%), hallucinations (34.7% vs. 13.6%), agitation (43.5% vs. 18.2%), delusions (21.7% vs. 13.6%), and aberrant motor behavior (34.7% vs. 9.1%). In general, many NPS are most common and severe in PDD patients, when compared to PD-CN, except for depression and anxiety, which can arise from early stages of PD21. In addition, apathy, anxiety, and depression are the three most commonly reported symptoms in patients with PD-CN, PD-MCI, and PDD; with prevalence for each symptom of approximately 50% out of all the cases (except for depression in PDD)[21-25]. In this regard, we found that the frequency of appetite and sleep disorders, assessed by

the NPI, was relatively higher in PDD patients compared to earlier stages of PD, a finding rarely reported[25]. However, studies comparing NPS frequency in patients with PDD and Alzheimer's disease (AD) have shown that apathy, agitation, disinhibition, and irritability were more common in patients with AD than in patients with PDD[27]; and other studies have found that disinhibition and irritability were more common in EA, and apathy was in PDD; while prevalence of agitation was similar in both groups[28]. Hallucinations were more frequent in PDD than in EA (49.6% vs. 21%)[27,28], and for a long time it was attributed to dopaminergic treatment[29], but has recently been linked to degenerative process rather than the use of medication[30,31].

Our study is subject to certain limitations: firstly, our results are not representative of Peruvian population, thus this sample is based on the reference center, and the overall measurement of NPS (according to the NPI) assesses symptoms of the last 30 days, and this may underestimate the cumulative prevalence of NPS in the course of PD evolution. Besides, this is not a longitudinal study; therefore, we can not determine risk factors for developing NPS. Secondly, the influence of medication on cognition or NPS is difficult to assess in cross-sectional studies such as ours. Thirdly, the NPS were evaluated according to the report of caregivers, so some subjective symptoms or those ones which may have been self-reported, have not been considered. Finally, patients were not evaluated by a psychiatrist in order to determine accurately the presence and severity of the NPS found in the questionnaire.

In conclusion, this study reproduces and extends previous findings of high prevalence of NPS among PD patients, and draws attention to analyze the full spectrum of PD behavioral characteristics from early stages. The systematic recognition of the presence and severity of comorbid neuropsychiatric conditions in PD can help the specialist both in the clinical management of the disease and to improve the quality of life of patients and their caregivers.

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None.

CONFLICTS OF INTEREST

The authors report no conflict of interest regarding this manuscript.

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Correspondence:
Nilton Custodio
Clínica Internacional
Avenida Garcilaso de la Vega 1420. Lima, Perú.
Phone: (51 1) 619 6161 anexo: 5004
Fax: (51 1) 431 9677
Cell phone: (51) 992509235
E-mail: niltoncustodio@neuroconsultas.com