

Neuropsychiatric symptoms and associated caregiver stress in geriatric patients with Parkinson's disease

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Abstract

Objectives: In Parkinson's disease, researchers are becoming increasingly aware of the need to include the assessment of behavioural and psychological symptoms as important outcome measures in clinical trials. Besides, clinicians are starting to recognise the need to identify and manage these symptoms in addition to the motor ones. Our objective is to explore the presence of neuropsychiatric symptoms in geriatric patients with Parkinson and the associated distress in their caregivers.

Methods: 100 patients with PD ageing 75 years old or more (50 PD without dementia and 50 PD Dementia (PDD)) were assessed using the 10-item Neuropsychiatric Inventory-questionnaire (NPI-Q), and the NPI Caregiver Distress Scale (NPI-D).

Results: The mean total NPI score was 12.9. At least one neuropsychiatric symptom was present in more than 80% of participants. Within PDD patients about 89% suffered at least one NPI symptom, 70% suffered at least 2 symptoms and one of those symptoms had an intensity scoring 4 or higher in more than 50%. Numbers in PD patients without dementia were significantly lower, though more than 50% of patients had at least 2 symptoms. The most frequent symptom was depression, followed by apathy, anxiety, depression and hallucinations. Antiparkinsonian agents can exacerbate psychotic symptoms. Nearly 60% of caregivers reported suffering a moderate to severe level of stress due to these symptoms. Symptoms causing more stress were agitation/aggression followed by hallucinations and irritability/lability.

Conclusions: Neuropsychiatric symptoms are frequent in geriatric patients with PD –specially in patients with PDD– and lead to moderate to severe caregiver distress.

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Introduction

Frequent neuropsychiatric symptoms have been reported in patients with neurodegenerative disorders, especially in Alzheimer's and Lewy Bodies diseases, but also in PD. According to Aarsland, up to 89% of patients with PD have at least one NPI symptom and 77% have two or more (1). Researchers are becoming increasingly aware of the need to include the assessment of behavioural and psychological symptoms as important outcome measures in clinical trials in Parkinson's disease (PD). Besides, clinicians are starting to recognise the need to identify and manage these symptoms early in addition to the motor ones.

Neuropsychiatric disturbances in PD patients contribute considerably to reduce quality of life and increase both the distress for the caregiver and the risk of admission to nursing home. While PD can coexist with other common causes of dementia, such as Alzheimer disease (AD) and vascular dementia (VD), dementia is increasingly recognised as a common feature of Parkinson disease itself. What is more, cognitive dysfunction is present in many patients without dementia (2) as it also happens in other alpha-synucleinopathies (3). Additionally, most patients with PD will eventually develop dementia, and previous studies found neuropsychiatric symptoms are more common and severe in PD when dementia is present (PDD) (4).

Since neuropsychiatric symptoms in elderly patients have profound effects in their lives –and their caregivers– a detailed knowledge of these symptoms is needed to identify and manage them accurately. In spite of all epidemiological studies during recent years, to the best of our knowledge, no studies have

specifically explored these symptoms in geriatric patients with PD or the associated stress in their caregivers. To reach this objective we administered the Neuropsychiatric Inventory (NPI-D and NPI-Q) to a sample of geriatric patients with PD and their caregivers. The validity of the NPI has been established, and high reliability in PD has been reported (5).

Methods

Patients

Patients were recruited from the Neurology and Geriatrics Units at *Hospital Álvarez-Buylla* (Mieres, Spain). Approval ethics committee at Hospital Universitario Central de Asturias was obtained. We invited to enrol consecutive patients meeting the inclusion criteria, up to completing the sample (100 patients). We screened patients ageing at least 75 years old diagnosed with PD according to the UK Parkinson's Disease Brain Bank criteria (6). They were both patients without dementia (n=50) and patients with mild to moderately severe dementia (n=50) as defined by the Movement Disorder Society (7,8). In patients with PDD, the onset of dementia was required to appear at least 2 years after the diagnosis of idiopathic PD. Patients were also required to have contact with a responsible caregiver at least 4 days a week. Exclusion criteria included any primary neurodegenerative disorder other than PD or any other causes of dementia, a history of alcohol abuse, and any disability or unstable disease that might prevent the patient from completing all study requirements. Participants and their caregivers gave informed consent.

Clinical Evaluation

Neuropsychiatric symptoms in patients and the impact on stress of caregivers were assessed using the Brief Clinical Form of the Neuropsychiatric Inventory (NPI-Q) (9) and the Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D) (10). Each domain of the NPI-Q is rated for frequency (1–4) and severity (1–3), and the overall score for a domain is the product of frequency and severity. On the NPI-D, each domain is rated for level of caregiver distress (level of distress: 0; not at all, 1; minimal, 2; moderate, 3; severe, 4; very severe or extreme distress, 5). The NPI total scores are the sum of the individual domain scores, with higher scores indicating more serious behavioural symptoms (NPI-Q) or greater caregiver distress (NPI-D). No cut-point or reference values exist for this scale.

Cognition was assessed by means of Mini Mental State Examination (MMSE) (11) and Frontal Assessment Battery (FAB) (12). Staging of PD was assessed by the Hoehn and Yahr scale (13). Pharmacologic treatment with antiparkinsonian agents and psychotropic drugs was recorded.

Statistical Analyses

Descriptive statistics were applied first (mean, standard deviation (SD), rates) for sample description. Student's *t* test was used for comparisons of normally distributed continuous data and χ^2 test for categorical variables. Non-parametric tests were used for comparison of the NPI scores owing to the skewness and non-linearity of these data. A value of $p < 0.05$ was considered significant.

Results

Sample Characteristics

NPI was completed for 100 patients (56% men and 44% women). The age of the sample -mean (SD)- was 81.94 (3.61) years, and they had 6.00 (5.06) years of formal education. The duration since onset of PD was 9.03 (5.9) years, and since diag-

nosis of dementia was 4.15 (2.7) years. The MMSE score was 18.23 (4.90), FAB 11.12 (2.4) and Hoehn and Yahr stage 2.84 (0.83). All patients were on antiparkinsonian agents, 39.4% used cholinesterase inhibitors, 34.4% used antipsychotic agents, 21.6% used antidepressants and 20.5% used anxiolytic agents. 19.1% used more than one type of psychotropic drug apart from antiparkinsonian agents.

Caregivers were family members in 87% of cases (spouse 47%, daughter 18%, son 12%, DAUGHTER-IN-LAW 8%, son-in-law 2%), while 13% were professional caregivers.

NPI-Q Scores in Patients

The mean (SD) total NPI score was 12.9 (12.0). The most prevalent symptoms were depression (53%), apathy (50%), anxiety (45%) and hallucinations (41%) (**Figure 1**). Patients with dementia had more neuropsychiatric symptoms than patients without dementia ($p = 0.03$). Eighty-one per cent (81%) PDD patients presented at least one, 70% had two or more symptoms and 56% had at least one symptom with a score ≥ 4 . Numbers in PD patients without dementia were significantly lower, though more than 50% of patients had 2 symptoms at least (**Figure 1**).

Associations between NPI-Q and Clinical Characteristics

The total NPI-Q score did not differ between male and female patients ($p = 0.55$), and we found no statistical association with age ($r = -0.18$; $p = 0.08$). However, we found significant associations between total NPI score and cognitive impairment ($p = 0.04$) and stage ($p = 0.04$). Patients with a MMSE score below the median score of 18 had more neuropsychiatric symptoms than those with MMSE score > 20 : mean total NPI 15.02 (13.23) ν 11.19 (10.71); number of symptoms 3.7 (2.3) ν 3.0 (2.0); Mann-Whitney test; $p = 0.04$ for both).

A similar pattern was found in the relationship between NPI items and Hoehn and Yahr stage.

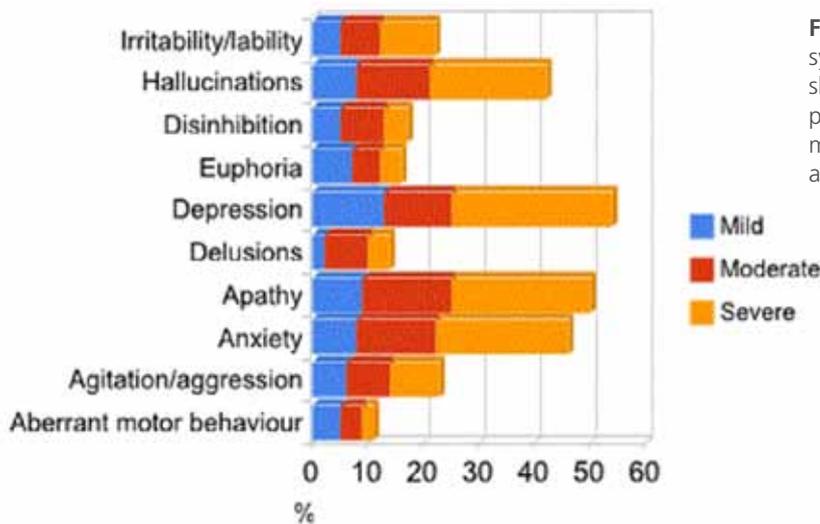
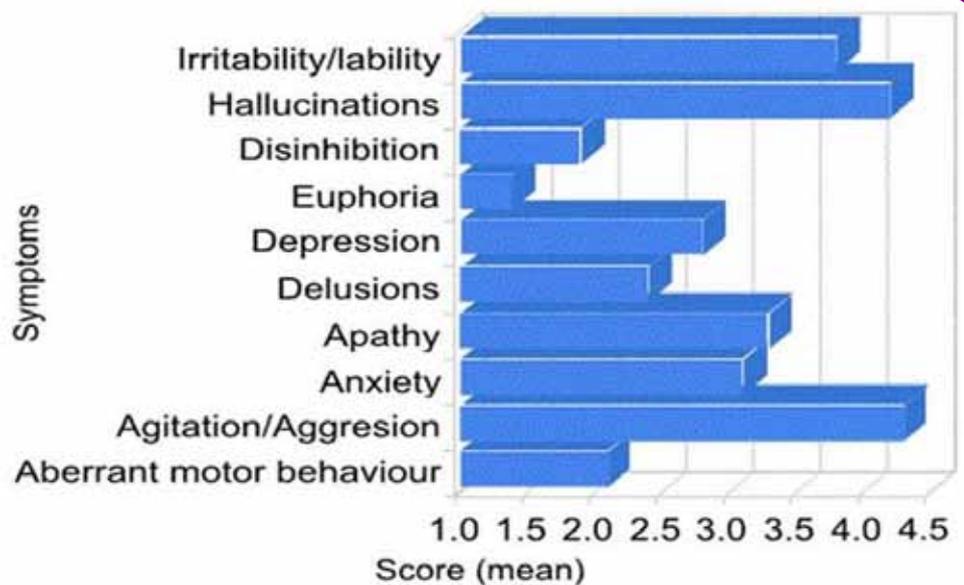


Figure 1. Prevalence and severity of neuropsychiatric symptoms in geriatric patients with PD. This figure shows results for the entire sample, including both patients with dementia and without dementia. The most prevalent symptoms were depression (53%), apathy (50%), anxiety (45%) and hallucinations (41%).

Figure 2. Caregivers stress reported as caused for neuropsychiatric symptoms. The highest caregiver distress score was found to be caused for agitation/aggression, followed by hallucination and irritability/lability.



Those with a Hoehn and Yahr stage at or above the median stage of 3 had a total NPI score of 15.33 (11.14) compared with 10.15 (11.50) in those with a Hoehn and Yahr score <3 ($p < 0.02$).

A significant and direct correlation between symptoms and doses of antiparkinsonian agents was found both for agonists and levodopa: the higher doses the more severe symptoms ($r = 0.88$; $p = 0.03$).

NPI-D scores in Caregivers

58.6% of the caregivers reported at least one NPI symptom leading to moderate severe stress, that is, a score of ≥ 3 . The highest caregiver distress score was found to be caused for agitation, hallucination and irritability (Figure 2). Carers of PDD patients suffered more stress than those of patients without dementia ($p = 0.02$) (Figure 2).

Discussion

Though PD was reported to be the synucleopathy with less cognitive impairment and neuropsychiatric symptoms between all synucleopathies (14), in recent years, many studies reported high prevalence of these symptoms in PD patients (3,15). In this study, we explored the presence of neuropsychiatric symptoms in a geriatric sample of patients with PD, both demented and non demented. At least one neuropsychiatric symptom was present in more than 80% of participants. Although some patients had few symptoms and low scores, a considerable number of patients had many symptoms, and 64% had a composite score of ≥ 4 for at least one item, indicating at least moderate severity. The most frequent symptom was depression followed by anxiety, apathy and hallucinations. These numbers are similar to Aarsland's in patients with PD of any age, confirming these symptoms are prevalent in any PD population, regardless of its age. However in patients with early untreated PD, hallucinations were much less prevalent (16), suggesting that probably both age and dopaminergic agents are risk factors for suffering hallucinations. On the other hand, anxiety disorders decrease with age (35).

The frequency and severity of psychiatric symptoms in the PDD group were even higher than those reported in clinical trials for PDD (17,18) and the distribution of psychiatric symptoms differed markedly between PDD patients and patients with moderate to severe AD (19), including our own cohort (20). Hallucinations were more severe in PD patients, while aberrant motor behaviour, agitation, disinhibition, irritability and euphoria were more severe in AD. In PDD, apathy was more common in mild Hoehn and Yahr stages, while delusions increased with more severe motor and cognitive disturbances. In PDD, only delusions correlated with the MMSE score. The cause for this difference may lie in differential pathophysiology, as suggested by recent findings on morphological and neurochemical sub-

strates of delusions and hallucinations in dementia with Lewy bodies, a disorder with clinical and neurobiological similarities to PDD (6, 21). Thus, the brain changes underlying psychosis in AD may differ from those in PDD, as has previously been shown for dementia with Lewy bodies and AD (22).

Depression occurs in more than a half of geriatric PD patients and is associated with a range of comorbidities and leads to decreased quality of life (23). The profile of depressive symptoms in PD differs from that in depressed subjects without PD since patients with PD showed significant less reported sadness, less anhedonia, less feelings of guilt and, slightly less loss of energy, but more concentration problems than depressed control subjects (24). It may be predictive of cognitive decline (25), though a recent study shows that is apathy and not depression the symptom associated with deficit in implementing efficient cognitive strategies (26). Controversially, in the Norwegian ParkWest study, apathy was significantly associated with male gender, higher depression scores and more severe motor symptoms, but was not with greater cognitive impairment. When excluding patients with significant depressive symptoms, apathy remained significantly associated with motor severity, suggesting a common underlying pathophysiological mechanism (27). Progression of motor signs predominantly mediated by non-dopaminergic systems (speech and axial impairment) may be a useful preclinical marker for incident apathy in PD (28).

Psychosis is a frequent complication of PD, and it is characterized mainly by visual hallucinations and delusions, which are often paranoid in flavour. Hallucinations are the most common manifestation, and they affect up to 40 percent of patients, particularly those with dementia (29,30). As we saw, the prevalence and severity of hallucinations in PD is higher in elderly patients, progressing over time. In non-demented PD patients, those with hallucinations are more likely to develop dementia than patients without this symptom (31,32) thereby announcing

dementia in many cases. Other manifestations of psychosis in PD include delusions, often paranoid and related to spousal infidelity and persecution (33).

A variety of antiparkinsonian agents, most notably anticholinergic agents, dopaminergic agents, and amantadine, can exacerbate neuropsychiatric symptoms in general, specially psychotic symptoms as visual hallucinations (34). All the antiparkinsonian drugs can give rise to hallucinations and psychosis, but the dopamine agonists are the ones with the greatest capacity to do so. Geriatric patients are even more sensitive to these drugs and especial caution is needed when using antiparkinsonian drugs in geriatric PD patients.

Panic disorder, generalised anxiety disorder and social phobia are prevalent anxiety disorders in PD (35). Comorbid depression with anxiety is frequently observed (36). The severity but not the duration of PD is positively related to anxiety. Anxiety disorders decrease with age and young onset PD patients are more likely to experience anxiety than the late onset ones (35).

Besides being common, the relevance of neuropsychiatric symptoms in geriatric patients with PD is further underlined by the finding that nearly 60% of the caregivers reported at least one NPI symptom leading to moderate or severe distress. However, the symptoms related with a more important contribution to caregiver stress are not the more frequent in patients, those are agitation/aggression, hallucinations and irritability/lability. This means that some symptoms (mood and anxiety disorders) do not lead to as much stress in caregivers of geriatric PD patients as behavioural symptoms do. Although some other studies failed to identify stress in caregivers derived from neuropsychiatric symptoms (37), more extensive studies also found this association, specially for those patients with dementia (38). An interesting study examined the level of agreement between caregiver and PD patient reports of neuropsychiatric problems reporting

a low level of agreement (39). This may represent patients do not live these problems the same way their carers do. This correlates with the fact that in our study the more frequent and severe symptoms in the NPI-Q are not those with the higher score in the NPI-D. In the Norwegian ParkWest study, focused on newly diagnosed PD, the symptoms leading to caregiver stress are exactly the same that we found as more frequent in geriatric patients (40). Thus suggesting that, in early stages, the symptoms leading to caregiver stress are the more prevalent ones, while the relative influence of symptoms on caregiver stress changes with time when the disease evolves and psychotic and behavioural symptoms are more severe.

Conclusions

In conclusion, we found a high prevalence of neuropsychiatric symptoms in geriatric PD patients. These symptoms lead to moderate to severe stress in their caregivers. The profile of these symptoms differs from that in other types of dementia as AD but is similar to the youngest PD patients. Our findings have implications for the appreciation, understanding and management of geriatric patients and their carers.

Competing interests

The authors declare that they have no competing interests.

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