

The prevalence and determinants of neuropsychiatric symptoms in late-stage parkinsonism

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Abstract

Background Late-stage Parkinsonism (PD) is an insufficiently studied population. Whilst neuropsychiatric symptoms, e.g. psychosis, depression, anxiety and behavioural problems, are frequently present, their prevalence and clinical predictors remain unknown. **Objective:** to determine the prevalence and predictors of neuropsychiatric symptoms in late-stage PD. **Methods** We conducted a multinational study of patients with PD with ≥ 7 years disease duration and either a Hoehn and Yahr stage ≥ 4 or a Schwab and England score $\leq 50\%$ in the "ON" stage. Neuropsychiatric symptoms were assessed through interviews with carers using the Neuropsychiatric Inventory (NPI), with frequency x severity score ≥ 4 indicating clinically relevant symptoms. Determinants analysed were demographic characteristics, medication, and motor and non-motor symptoms. Univariate and multivariate logistic analyses were performed on predictors of clinically relevant neuropsychiatric symptoms. **Results** Six hundred and twenty-five patients were recruited in whom the NPI could be completed. In 92.2% (576/625) of patients, at least one neuropsychiatric symptom was present and 75.5% (472/625) had ≥ 1 clinically relevant symptom. The most common clinically relevant symptoms were: apathy (n=242; 38.9%), depression (n=213; 34.5%) and anxiety (n=148; 23.8%). The multivariate analysis revealed unique sets of predictors for each symptom, particularly the presence of other neuropsychiatric features, cognitive impairment, daytime sleepiness. **Conclusion** Neuropsychiatric symptoms are common in late-stage PD. The strongest predictors are presence of other neuropsychiatric symptoms. Clinicians involved in the care for patients with late-stage PD should be aware of these symptoms in this specific disease group and pro-actively explore other psychiatric comorbidities once a neuropsychiatric symptom is recognized.

Late-stage Parkinsonism (PD) is defined as a phase when patients have become dependent on caregivers for activities of daily living (1). Patients with late-stage PD experience multiple motor symptoms and non-motor symptoms (1-3), including neuropsychiatric symptoms (NPS) such as psychosis, depression, anxiety, apathy and behavioural problems. The presence of NPS is associated with a decreased quality of life, increased caregiver burden and an increased risk of institutionalization (4-7). Two small cohort studies suggest NPS to be highly prevalent in late-stage PD (2, 3). In the first study in a cohort of 73 nursing home residents, the most frequent symptoms were depression (52.9%), irritability (42.0%), apathy (30.0%) and anxiety (28.6%) (3). In the second study, in an outpatient cohort of 50 late-stage PD patients, depression was also the most commonly encountered symptom (62%), with anxiety (50%) and visual hallucinations (44%) also often being present (2). However, information on the prevalence and correlates of NPS in this population is limited. Depression in PD overall is associated with earlier age at onset and younger age, presence of cognitive impairment, freezing of gait, levodopa-induced dyskinesia (LID), motor-defined 'off'-state, pain and problems with sleep (8-13). Psychotic symptoms, including hallucinations and delusions, are more prevalent in patients with longer disease duration, advanced disease stage and presence of dementia (14, 15). Also, treatment with dopaminergic medication can trigger psychotic symptoms (14, 16). However, studies on the determinants of NPS were conducted either in cohorts of patients with short disease duration (10, 12, 13, 17-19), excluded patients with cognitive impairment (11, 20), focused solely on demented patients (4, 21) or did not include patient-related factors in the multivariate analyses. The aim of this study was to assess the prevalence and clinical predictors of NPS in the overall group of patients with late-stage PD.

Methods

Study design

We examined the prevalence and correlates of NPS in patients in the Care of Late-Stage Parkinsonism-cohort (CLaSP-study), which is a longitudinal cohort study aimed to evaluate the needs of patients in late-stage PD. This paper presents a detailed analysis of the extensive baseline measurements. Further details of the study have been described in full detail elsewhere (22). In brief, CLaSP included centres in London (United Kingdom), Lund (Sweden), Munich (Germany), Marburg (Germany), Nijmegen (The Netherlands), Bordeaux (France) and Lisbon (Portugal), and included patients with (a) a clinical diagnosis of Parkinsonism, (b) a disease duration of at least 7 years and (c) a Hoehn and Yahr stage 4 or 5 in “ON”-stage (23) or a score on the Schwab and England scale of 50% or less in “ON”-stage (24). Patients with slowly progressive atypical Parkinsonism were not excluded as differentiating distinct Parkinson syndromes is typically difficult in late-stage disease and health care needs and provision are likely very similar. Exclusion criteria were: (1) a clear history of dementia prior to the onset of parkinsonism, and (2) diagnosis of “symptomatic parkinsonism”, such as normal pressure hydrocephalus and drug-induced parkinsonism. Trained assessors collected the data during home visits or outpatient appointments. All clinical data were entered in a certified data management system. The study was conducted in compliance with the Helsinki Declaration and approved by the ethical committees of all participating study sites (London: Camden and Islington NRES Committee 14/LO/0612, Bordeaux: South West and Overseas Protection Committee III (South West and Overseas Protection Committee). 2014-A01501–46, Lisbon: Centro Hospitalar Lisboa Norte, DIRCLN-19SET2014–275, Lund: EPN Regionala etikprovningnamnden: Lund (EPN Regional Ethics Name: Lund). JPND NC 559–002, Marburg: Ethik-Kommission bei der Landesärztekammer Hessen (Ethics Commission at the State Medical Association Hesse). MC 309/2014, Munich: Ethikkommission bei der LMU Munchen (Ethics committee at the LMU Munchen). 193–14, Nijmegen: Radboud universitair medisch centrum, Concernstaf Kwaliteit en Veiligheid, Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen (Radboud university medical center, Group staff Quality and Safety Human Research Committee, Arnhem-Nijmegen region). DJ/CMO300). To obtain consent detailed oral and written information were given to the patients and their informant to ensure that the patient fully understands potential

risks and benefits of the study. If patients were unable, consent was obtained with the legal representative, in accordance with national law. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Assessments

NPS were assessed with the Neuropsychiatric Inventory – Nursing home version (NPI) (25). The NPI was originally developed for use in research with dementia patients and was suggested for use in PD-patients to assess NPS by the Movement Disorder Society (26). The NPI scores 10 NPS: delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, and two items associated with NPS: sleep disturbances and appetite/eating changes. Each item is scored in an interview with a carer for frequency and severity on a Likert scale ranging from 0-4 and from 0-3 respectively, with higher scores indicating higher frequency or higher severity. Multiplying frequency with severity scores produces a composite score ranging from 0-12. NPS with a composite score ≥ 4 are considered clinically relevant (27, 28).

Demographic, disease- or treatment related variables that were considered as potential predictors of NPS in PD included age, gender, years of education, disease duration, disease severity, co-morbidity, and a range of motor and non-motor features (see table 1). Disease severity was assessed using Hoehn and Yahr stage (23). Motor function was measured with the Unified Parkinson Disease Rating Scale – part 3 (UPDRS-III) (24). The UPDRS-III consist of 14 items, from which subscores were derived for speech (item 18), facial expression (item 19), tremor (item 20 and 21), rigidity (item 22), bradykinesia (items 23-26), postural instability and gait impairment (PIGD; items 27-29) and body hypokinesia (item 30) (29). The Mini-Mental State examination (MMSE) (30), clock drawing test and verbal fluency were used for assessment of cognitive performance. Activities of daily living were assessed with the UPDRS – part 2 (UPDRS-II) (24). Treatment complications were measured with the UPDRS – part 4 (UPDRS-IV), which were summarized for LID (items 32-34) and off-periods (items 36-39) (24). NPI-items other than the dependent variable were used as independent variables. Other non-motor features were

measured with the non-motor symptoms scale (NMSS) in the domains 1) cardiovascular, 2) sleep/fatigue, 6) gastrointestinal tract, 7) urinary, 8) sexual function and 9) miscellaneous (31). The NMSS measures a composite of severity (0-3) x frequency (0-4) for each item. Co-morbid diseases were assessed using the Charlson Comorbidity Index (32). The dopaminergic medications were recalculated to levodopa equivalent daily doses (LEDD) (33). Psychotropic drug use was collected for antidepressants, antipsychotics, anti-dementia drugs, anxiolytics and hypnotics.

Statistical analysis

Results were first examined for missing data. Variables were excluded from further analysis when >20% of the data was missing. To reduce missing data, imputation techniques were used for the UPDRS and NMSSs. According to published recommendations (34), items were substituted with case-specific means on the UPDRS-I and UPDRS-II if one item was missing and on the UPDRS-III if 7 or less items were missing. On the NMSSs, sensitivity analyses were performed to choose an imputation strategy. The case-specific mean of the entire scale yielded the highest number of substitutions without changing the summary data scores (means, medians and measures of variance) of the total sample, and this strategy was therefore chosen as the imputation strategy.

Prevalence of individual NPS is presented as frequencies and percentage of the total sample of those with NPI data. For the determinant analysis, both univariate analysis and multivariate logistic regression analysis were performed with the presence of clinically relevant NPS as the dependent variable (35). Univariate between-group differences were evaluated with an unpaired samples T-test for normally distributed variables and the Mann-Whitney test for non-normally distributed variables. Categorical variables were evaluated with the chi-square test. Independent variables with an association with the dependent variable with a p-value ≤ 0.1 in the univariate test were included in the multivariate models. To prevent collinearity, bivariate correlation coefficients were calculated between these included independent variables. If variables had a rho > 0.5 , only the variable with the highest correlation with the dependent variable was included in the multivariate model. In the

multivariate analysis a backward stepping selection procedure was applied with entry $p < 0.05$, removal $p < 0.10$, classification cut-off 0.5 and maximum 20 iteration. Descriptives are reported with mean and standard deviation for normally-distributed variables and with median and minimal-maximal values for non-normally distributed variables. Results were considered statistically significant if the Bonferroni-corrected $p < 0.05$. All analysis was performed using SPSS 22.0 (IBM, Armonk, NY).

Results

The clinical characteristics of the participants with completed NPI-scores ($N=625$) are given in table 2. Data was missing $\geq 20\%$ for the Verbal fluency, Clock Drawing test, and Charlson Comorbidity score, which were therefore excluded from analysis. On the NPI missing data ranged from 69 (10.0%) for hallucinations to 78 (11.3%) for aberrant motor behaviour. Elation and disinhibition had a prevalence lower than 5% in the total sample and therefore were not analysed further. The most common reason for missing data was the absence of a (informal) caregiver to complete the information, which is required for the application of this scale ($n=53$). Those participants who missed all NPI items ($n=67$; 9.7%) were younger (median age 75 vs. 77 years; $p < 0.01$), had better cognitive performance (median MMSE total 25 vs. 24; $p=0.01$) and had lower doses of dopaminergic medication (median LEDD 687.5 vs. 815; $p < 0.01$). No differences were found on disease duration, gender, Hoehn and Yahr stage and Schwab and England score. There were no missing data for age, medication use and Hoehn and Yahr stage.

Prevalence of NPS

In 92.2% (576/625) of the participants at least one of the NPS was present and at least one of the clinically relevant NPS was present in 75.5% (472/625) of the participants (table 3). The median number of NPS in each patient was three and of clinically relevant NPS two per patient. The most frequent NPS on the NPI were depression ($n=372$; 60.2%), apathy ($n=309$; 49.7%) and anxiety ($n=274$;

44.1%), and the most frequent clinically relevant symptoms were apathy (n= 242; 38.9%), depression (n=213; 34.5%) and anxiety (n=148; 23.8%).

Determinant analysis

Results of the univariate test are shown in the supplementary appendix B. In the multivariate analyses (table 4-7), for most NPS, the strongest associations were seen with other NPS. The presence of hallucinations was predicted by the presence of delusions (OR 1.482; Wald = 44.60 $p<0.001$), and conversely the presence of delusion was predicted by the presence of hallucinations (OR 1.454; Wald = 69.76; $p<0.001$). Agitation was predicted by severity of irritability (OR 1.551; Wald = 41.59; $p<0.001$) and depression (OR 1.196; Wald = 15.27; $p=0.002$), and conversely irritability was predicted by agitation scores (OR 1.410; Wald = 29.50; $p<0.001$) as well as anxiety (OR 1.163; Wald = 11.36; $p=0.01$).

In several models other predictors than NPS were found. The presence of hallucinations was inversely predicted by the degree of cognitive performance (OR 0.915; Wald = 17.07; $p<0.001$) and correlated positively with daytime sleepiness (OR 1.154; Wald = 15.42; $p=0.002$), For depression, the ability to undertake personal hygiene tasks (OR 1.641; Wald = 15.33; $p=0.003$), sleep problems (OR 1.100; Wald = 7.67; $p=0.006$) and weight loss (OR 1.115; Wald = 11.24; $p=0.02$) were the strongest ~~determinants~~predictors, in addition to two NPS: anxiety (OR 1.332; Wald = 36.97; $p=<0.001$) and apathy (OR 1.669; Wald = 21.12; $p<0.001$). For anxiety, the main predictor variables were loss of interest in sex (OR 1.094; Wald = 13.83; $p =0.005$) and again two NPS: depression (OR 1.264; Wald = 33.79; $p<0.001$) and irritability (OR 1.210; Wald = 10.57; $p =0.03$). For apathy, the strongest determinants were a lower cognitive performance (OR 0.886; Wald = 39.23; $p<0.001$), loss of interest in sex (OR 1.091; Wald = 14.14; $p=0.005$) and the presence of depression (OR 1.180; Wald = 16.05; $p =0.002$). For aberrant motor behavior, LID was the strongest predictor (OR 1.243; Wald = 12.56; $p=0.008$), followed by the presence of delusion (OR 1.186; Wald = 10.63; $p=0.02$).

Discussion

We found that NPS are highly prevalent in the late-stage of PD, and that these are clinically relevant in the vast majority of patients. Most patients had at least two NPS occurring together. Although each NPS has a unique set of disease-related determinants, the strongest predictors for most NPS were the presence of other NPS.

Multiple prevalence estimates of NPS in PD have been published, ranging from 14% to 69% for individual NPS and 61% to 89% for overall presence of any NPS (8, 36-42), but there are no previous studies examining their combined prevalence in the overall late-stage disease population. While there are publications available for cohorts of patients with Parkinson dementia (27) and long disease durations (43), late-stage Parkinsonism differs as it is defined by the notion of having become dependent on others for daily living (1). These patients have, by nature of their dependencies, difficulty in participating with study protocol and visits, and do not frequently ~~do not~~ participate in studies. Earlier studies in this population did not have appropriate sample sizes to definitely answer our research questions (sample size <100) (2, 3). Our high prevalence figures for NPS do resemble the prevalence of NPS in a cohort with 537 PD dementia (PDD) participants (4, 44) in whom prevalence of hallucinations, depression and apathy was 44%, 57% and 54%, respectively (4). That study recruited participants from a multicentre trial on rivastigmine, using the presence of mild to moderate severe dementia (MMSE 10-24) as inclusion criterion. In the current study of patients with late-stage PD, in whom 36% had a self-reported diagnosis of dementia and 53% had cognitive impairment as defined by a MMSE<26, the corresponding rate of hallucinations, depression and apathy were very similar at 41%, 60% and 50%. The percentage of clinically relevant symptoms in our study is also similar to the findings in the PDD cohort, with the exception of clinically relevant depression and aberrant motor behaviour, which were slightly higher in our late-stage PD population (35% vs. PDD 21% for depression, 18% vs. PDD 13% for aberrant motor behaviour). It is likely that there is considerable overlap between the two cohorts with comparable mechanisms, although our study selected participants primarily

based on motor stage and disease duration. Both cohorts share characteristics like worse cognitive performance, functional dependence, daytime sleepiness and motor complications. There is an ongoing controversy on the underlying pathology of PD dementia, which is likely to include diffuse Lewy body distribution in the cortical areas as well as Alzheimer pathology (45). Our results that NPS are very common in late-stage PD with and without dementia suggest that NPS are not necessarily restricted to those with dementia, but can be hypothesized to reflect the wider spread of pathology in all patients in late-stage PD.

Of note, the most consistent predictors of NPS in general was the presence of other NPS. This association may suggest that these determine each other, such as a depression resulting from hallucinations, but more likely suggest that they are manifestations of the same syndrome, e.g. anxiety and depression, or a common aetiology due to jointly affected brain regions. Multiple studies have investigated the complex interrelationship of NPS in PD, using factor and hierarchical cluster analyses (4, 18, 40, 46, 47). In the earlier mentioned cohort of PDD, five NPS separate profiles were suggested: 1. low overall NPI scores; 2. high depression, anxiety and apathy scores and low scores on other NPS items; 3. high apathy scores and low scores on other NPS items; 4. high scores on all items, especially on agitation and irritability; and 5. high scores on hallucinations and delusion and low score on other items. Our results in the late-stage PD patient population are in keeping with these profiles with an interrelation between depression, anxiety and apathy (profile 2); correlation between irritability, agitation, anxiety and apathy (profile 4); and correlation between delusion and hallucinations (profile 5). However, we have not performed cluster analysis to confirm these findings as it was outside the scope of the current study. Other associations in this study are in keeping with the different expressions of NPS, concomitant cognitive impairment or medication side effects, such as the association of depression with agitation, or association of delusions with aberrant motor behaviour. We also found an association of aberrant motor behaviour with LID. Whilst aberrant motor behavior is largely defined by repetitive tasks such as pacing and undoing buttons, there is also overlap with LID and an urge to move (48). Another explanation for this association is that late-stage PD patients may

not be able to display aberrant motor behaviour, due to severe motor impairment, with the exception of those that have a good motor response with LID and are able to display aberrant motor behaviour.

We also found an association between loss of libido and anxiety and apathy, which may be the result of the NPS itself, loss of libido leading to anxiety or the common underlying mechanism affecting related brain areas. Other results align with previously literature such as association of cognitive performance with hallucinations and apathy (49-51), the association of daytime sleepiness with hallucinations (52), the association of weight loss with depression (53, 54) and the findings of dependence in personal hygiene as determinant for depression (55).

It is noteworthy that, once other NPS are accounted for, in this population with virtually uniformly severe motor impairment, other motor and non-motor aspects of the disease were not strongly associated with the occurrence of NPS. Whilst some of this may be explained by lack of sensitivity of the rating scales used, it can be hypothesized that the pathology in other areas than those determining motor function is the overriding factor for the occurrence of these symptoms.

Strengths and limitations

This is the largest study to date in this difficult to reach population. We demonstrate the high prevalence and severity of NPS in this population. This study's limitations include the heterogeneity of the sample as we included patients with any type of parkinsonism. However, only a small percentage of patients did not have a diagnosis of PD (n=80; 12%) and the results restricted to those with a diagnosis of Parkinson's disease were similar. We allowed for the inclusion of patients already using psychotropic drugs. The current prevalence estimates could be an underestimation as a result of this. We did not include treatment variables in the analysis because these can be both causes and consequences of NPS. Therefore, no conclusions can be drawn on potential undertreatment with psychotropic drugs or on the contribution of specific dopaminergic treatments (like dopamine agonist). Another limitation is the cross-sectional design of the study. As a result of this, we cannot infer the causality between determinant and outcome. The number of patients with dementia or cognitive

decline is relatively low compared to another cohort with similar disease duration(56, 57). This could indicate a recruitment bias where patients with dementia were less likely to participate. On the other hand, one of the key strengths of the study includes its size and the strong efforts to include patients not currently in specialist care. Due to the nature of the condition, our selection criteria and the primary assessment measure of NPS requiring a carer, we were at risk of being unable to complete the assessment in several participants, resulting in missing data. In order to mitigate this, we took considerable care to allow for frequent breaks in the assessment and spreading of assessments across multiple visits. We further performed an elaborate missing data analysis prior to analysis to ensure participants and variables were included where possible. We believe that these steps allowed for a high study quality despite the challenges of recruitment and assessment in this population.

We demonstrated that NPS are highly prevalent in late-stage PD and that they predict the presence of other NPS. Clinicians involved in the care for patients with late-stage PD should be aware of the frequent occurrence of NPS in this specific disease group and pro-actively explore other psychiatric comorbidity once NPS are recognized. Future research should work to shed more light on the common aetiology of NPS and develop tailored interventional and supportive strategies for this disease group.

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Authors' Roles

- 1) Research project: A. Conception, B. Organization, C. Execution;
- 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
- 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

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Supplementary materials

Frequencies of neuropsychiatric symptoms in the subgroup of patients with typical Parkinson's disease is shown in the supplemental appendix A. Also, univariate associations between the presence of neuropsychiatric symptoms and predictors are shown in the supplementary appendix B.

