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Neuropsychiatric symptoms in Serbian patients with Parkinson's disease

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ABSTRACT

Background: Parkinson's disease [PD] is associated with wide variety of neuropsychiatric symptoms, although it is primarily considered as a movement disorder.
Objective: To examine whether PD patients can be meaningfully classified into subgroups according to their neuropsychiatric symptoms, reported by their caregivers.
Methods: Three hundred and sixty PD patients [mean age = 63.5, SD = 10.3] from the academic clinical setting were assessed with the 12-subscale Neuropsychiatric Inventory Questionnaire [NPI]. A two-stage cluster analysis was used to identify the subgroups groups of patients with specific neuropsychiatric profile.
Results: Three hundred and twenty-one PD patients [89%] showed at least one psychiatric symptom. The most common symptoms were anxiety [73.1%], depression [64.7%], and apathy [51.7%], and nighttime disturbance [51.3%], whereas the least common were euphoria [0.3%], and delusions [1.7%]. The mean [SD] total NPI composite score was 16.9 [17.4]. Two hundred eight PD subjects [58%] of the total sample had at least one symptom with a score ≥4. Three clusters were identified: a] Cluster 1, with no or few NPI symptoms [n = 200; 55.6%]; b] Cluster 2, with mild to moderate symptoms on depression, anxiety and apathy scales [n = 140; 38.9%]; and c] Cluster 3 with high agitation, disinhibition and irritability scores [n = 20 patients; 5.6%]. PD subjects with clinically significant neuropsychiatric symptoms were older with more severe motor and cognitive impairment.
Conclusions: This study emphasizes the high prevalence and importance of neuropsychiatric symptoms in PD patients; therefore clinicians should also focus on treating in parallel with motor symptoms.

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1. Introduction

Prevalence of neuropsychiatric co-morbidities in Parkinson's disease [PD] varies widely among reported series due to increasing age of patients, duration of the disease, cognitive impairment and assessment tools [1–6]. Also, cultural, social and family structure might be responsible for differences [7–12].

Growing evidence indicated existence of PD subtypes based on associated neuropsychiatric and behavioral problems [5,6,13], either in the cohorts of the early stage "de novo" PD patients [14], or in those with dementia [13]. Neuropsychiatric symptoms (NPS) are part of the non-motor manifestation of PD, and have a significant impact on the quality of life [QoL] of PD patients, and on a caregiver burden and distress [presence of NPS apart from dementia is associated with caregiver distress] [8,15,16,17].

Therefore, in the present study we administered the Neuropsychiatric Inventory [NPI] [18], to evaluate the frequency of neuropsychiatric symptoms and accompanied caregiver distress in a representative sample of Serbian patients with PD, recruited at the academic tertiary clinical center. The NPI uses a screening strategy to minimize administration time, examining and scoring only those behavioral domains with positive responses to screening questions. Both the frequency and the severity of each behavior are determined. Information for the NPI is obtained from a caregiver familiar with the patient's behavior [18]. We expected

specific pattern of NPS and caregiver distress in our representative sample, taking in account that typical Serbian family system is enmeshed (an enmeshed relationship is characterized by an extreme amount of emotional closeness, loyalty and dependency on each other). We also explore whether natural subgroups of patients could be identified based on their neuropsychiatric profile.

2. Patients and methods

The study included 375 consecutive PD patients from the Department for Movement Disorders, Institute of Neurology, Clinical Center of Serbia [CCS], Belgrade; diagnosed according to the UK PD Brain Bank criteria [19]. The Ethical Committee of the CCS approved the present study. After completed informed consent, a semi-structured interview was performed to obtain information on patient's demographic variables [age, education, etc.], disease history and drug therapy. Patients were tested during the "on" time. The Mini-Mental State Examination [MMSE] was used to estimate global cognitive function [20]. The motor disability was estimated by the Hoehn and Yahr [HY] staging system [21], and with the Unified Parkinson's Disease Rating Scale motor part [UPDRS part III] [22]. From the UPDRS III items axial impairments [items: speech, facial expression, arising from chair, gait, posture, postural stability, body bradykinesia and hypokinesia] was derived and axial motor disability scores computed [23]. The patients were classified as having tremor-dominant (TD) versus non-TD, e.g. Postural Instability and Gait disturbance (PIGD); and Intermediate (IM) motor subtypes [24] (Jankovic et al., 1990). The neurologist [blind to the psychiatric data] assessed the patients about 1–2 h after they had taken their medication, during the maximal benefit of the medication.

The NPI profile for each patient was obtained following standard procedures. First, screening questions for each of the neuropsychiatric symptoms were asked. Positive responses were followed by subquestions. If the subquestions confirmed the screening question, the severity and frequency of the symptoms were determined according to the criteria provided for each domain. The informant rated the frequency of each symptom on a scale from 1 to 4, and the severity of the symptom from 1 to 3. A composite score [frequency × severity, yielding a score ranging from 1 to 12] for each scale was used further in the analyses. The NPI assesses the frequency and severity of 12 neuropsychiatric disturbances [delusions, hallucinations, agitation, dysphoria/depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, night-time disturbances and appetite/eating disturbances]. The total score of the NPI is the sum of the subscale scores. The NPI has been shown to have adequate test-retest and inter-rater reliability, as well as good concurrent validity with relevant behavioral scales [25,26].

Caregivers were requested to assess their level of emotional distress caused by each symptom [level of stress: 0 = not at all; 1 = minimally; 2 = mildly; 3 = moderately; 4 = severely; 5 = very severely or extremely stressed]. The total distress score was obtained by adding together the scores of the individual NPI distress questions.

Patients with suspected atypical parkinsonism [27–28]; and patients with global cognitive decline accomplishing criteria for Lewy body dementia [29], or cognitive decline due to other general medical condition (severe physical disease) according to DSM-IV were not included in the study.

3. Statistical analyses

In order to assign PD patients to subgroups/clusters on a basis of similarities in neuropsychiatric problems, we applied two-step clustering procedure using NPI symptoms assessments, taking into account that this clustering procedure handles large datasets and offer clustering criterion. This procedure uses an agglomerative hierarchical clustering method. The clusters were analyzed regarding the MMSE, L-dopa dosage, disease duration, axial motor disability score, and UPDRS [motor subscale] score. A one-way analysis of variance was used to determine on which of these variables subgroups/clusters of patients were significantly different. The correlations between caregiver distress parameters and NPI scores were also tested. Parametric Pearson correlations of total NPI scores [either NPI_12 item total score or NPI_10 item total score] with patient's age, UPDRS motor score, axial signs, age at onset, and duration of the disease were tested, as well. The association of NPI_10 and NPI_12 total item score with HY staging was tested with ANOVAs. All statistical analyses were performed using the SPSS version 17. Statistical significance was set at $p < 0.05$.

4. Results

Fifteen out of 375 patients were excluded from the study due to incomplete data set. Demographic and clinical data of remaining 360 PD patients are presented in Table 1. The total NPI_12 item score [mean ± SD] was 16.9 ± 17.4; and the NPI_10 item version score [two items referring to neurovegetative changes, night-time sleep and appetite/eating disturbances were omitted] was 13.3 ± 14.3.

The mean scores on each behavioral domain for whole sample of patients, percentage of patients who express at least one symptom [n = 321; 89%] by each behavioral domain; percentage of patients with a score ≥4 on each NPI domain and caregiver distress scores are shown in Table 2. Two hundred and sixty three patients [73.1%] were reported to have symptoms of anxiety on the NPI. Other most common symptoms were depression [n = 233 patients; 64.7%], apathy [n = 186 patients; 51.7%], and sleep disturbances [n = 181 patients; 51.3%], while the least common were euphoria [n = 1 patient; 0.3%], and delusions [n = 6 patients; 1.7%]. Higher caregivers' distress scores [>1] were associated with higher ratings on dysphoria/depression, anxiety, and apathy/indifference (see Table 2). Taking that the scores 1 or 2 on the NPI items may be clinically trivial [as it is previously suggested by Kulisevsky et al., 2008]; the further analyses were done with a score ≥4 on each NPI domain. Sixty-four percent of those who expressed at least one neuropsychiatric symptom [58% of the total sample] had at least one symptom with a score "≥4"; mostly for depression [38.3%], anxiety [37.3%] and apathy/indifference [36.9%]. In the subgroup with more severe neuropsychiatric symptoms, the most intensive caregiver distress [score ≥ 3] was recorded for delusions, agitation/aggression, disinhibition and aberrant motor behavior of PD patient (Table 2).

Correlation analyses showed significant association between the total NPI scores [either NPI_12 total score or NPI_10 total score] and age of patient [r = 0.16/or r = 0.15, p < 0.01]; duration of the disease [r = 0.17/or r = 0.18, p < 0.001]; UPDRS motor score [r = 0.51/or r = 0.49, p < 0.001]; axial motor disability score [r = 0.47/or r = 0.44, p < 0.001], but not with age at onset of the disease r = 0.071/r = 0.074 [p > 0.05]. The NPI_10 scores and NPI_12 score did differ

Table 1
Demographic and clinical characteristics of the PD patients.

Variable	Mean (SD)
n	360
Age (year)	63.5 (10.30)
Male %	65.0%
Education (year)	11.11 (4.11)
Disease duration (year)	7.23 (5.12)
UPDRS motor score	50.9 (23.51)
HY stage	
Mild (I–II)	54.2%
Moderate (III)	36.4%
Severe (IV–V)	9.4%
LED	573.81 (275.35)
MMSE score	26.07 (4.01)

UPDRS motor score, The Unified Parkinson's Disease Rating Scale motor part.
HY stage, Hoehn and Yahr staging scale.
MMSE, The Mini-Mental State Examination.
LED, Levodopa equivalent dose.