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# Nonmotor symptoms in de novo Parkinson disease comparing to normal aging

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ABSTRACT

*Objective:* Nonmotor symptoms (NMSs) are common in Parkinson disease (PD), affecting patient's quality of life. The prevalence and domains of NMSs in untreated de novo PD remains unclear, especially comparing to normal aging. The objective was to determine NMSs in untreated de novo PD patients.
*Patients and methods:* We performed a cross-sectional study to evaluate the frequency and severity of NMSs in untreated de novo PD patients (n = 71) and age-matched normal controls (n = 60) using the Non-Motor Symptoms Scale (NMSS). The motor section of the Unified Parkisnon Disease Rating Scale (mUPDRS) and the Hoehn and Yahr (HY) stage were also obtained in PD patients
*Results:* The number of NMSs and the NMSS scores were significantly higher in the PD patients than in controls ($p < 0.001$). There was no correlation of the NMSS scores with age and sex in both group and additionally with mUPDRS score and HY stage in PD patients group. Mood/cognition, attention/memory and gastrointestinal domains are the most frequent in PD patients and rarely seen in controls.
*Conclusion:* NMSs in untreated de novo PD patients are more prevalent and severe with different domain involvement comparing to normal aging.



## 1. Introduction

The Parkinson disease (PD) is one of the most common neurodegenerative brain disorders [1]. More recently, non-motor symptoms (NMS), such as psychiatric, sleep disorders, autonomic dysfunction symptoms and others, have been recognized as a potential cause of disability and deterioration of PD patients' quality of life [2–4]. NMS of PD occur throughout the disease course. There is evidence that certain NMS are present at disease onset or even may precede motor symptoms [5–8]. It has been suggested that some of the non-motor investigations could be added to support the diagnosis of Parkinson disease [8,9]. The prevalence and severity of non-motor symptoms in early PD (before initiation of antiparkinsonian drugs) remains unclear, especially comparing to healthy controls.

The Non-motor Symptoms Scale (NMSS) has been recently introduced to assess the frequency and severity of different domains of NMS in PD [10–12]. We developed a Croatian translation of the scale and report in this paper the results obtained in patients with PD compared to healthy controls.

## 2. Patients and methods

### 2.1. Study population

We performed a single-center cross-sectional study in 71 de novo PD patients recruited from our Outpatient Neurology Department and 60 age-matched apparently normal controls.

All patients had newly diagnosed PD defined according to the United Kingdom Brain Bank Criteria [13] with L-dopa exposure no longer than 2 weeks prior to study entry. Exclusion criteria were: severe vascular encephalopathy or normal pressure hydrocephalus; symptoms suggesting multiple system atrophy or progressive supranuclear palsy according to consensus criteria [14,15]; medication induced parkinsonism.

Controls were gathered from among the friends and relatives of patients who did not have any neurological disease on interview and examination and who had negative family history on idiopathic PD.

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All subjects had to be between 40 and 85 years old. Antipsychotic drugs were exclusion criteria for both groups. Subjects unable to read, understand or answer written questionnaires were excluded.

The Institutional Ethic Committee approved this study and informed consent was obtained from all of the subjects.

### 2.2. Investigations

Demographic variables and medical history, including current comorbidities and medications, were collected by interview from the patient and the patient's family. The modified Hoehn and Yahr (HY) scale [16] was used to assess overall disease severity, and the Unified Parkinson's Disease Rating Scale (UPDRS) part III was used to assess motor disability [17].

To evaluate non/motor clinical features, the Non Motor Symptoms Scale (NMSS) was administered. NMSS is composed of 30 items, each one assessed for severity (from 0 to 3) and frequency (from 1 to 4) and scored through the multiplication of both values (from 0 to 12). Items are collected in 9 domains (cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, others) and the maximum total score, indicative of higher severity and frequency of non-motor symptoms, is 360 [10]. The prevalence of each non-motor symptom as measured by the NMSS was obtained calculating the presence of each symptom if scoring 1 or more points on the NMSS. Additionally, the number of NMSs per subjects was evaluated in patients and controls.

We translated the original NMSS [10] to Croatian language and validated it using a translation-backtranslation protocol. The English scale was translated to Croatian and subsequently, this Croatian translation was back-translated to English independently by two individuals. The original English scale was compared with the two back-translated questionnaires and discrepancies were corrected by consensus between the people involved in the translation.

### 2.3. Statistics

The chi-square and Fisher's exact tests were used to compare the frequency of NMS in the 2 groups. Mean NMS scores were compared using the Mann–Whitney *U* test. Spearman's correlation coefficient was used for nonparametric correlations. Correlation coefficients more than 0.65 were arbitrarily chosen as indicative of strong correlations. Values less than 0.25 were considered indicative of negligible correlation, and those in between were taken as indicative of weak to moderate correlation. All P values below 0,05 were considered significant. IBM SPSS Statistics version 21 (www.spss.com) has been used in all statistical procedures.

## 3. Results

A total of 71 patients and 60 controls completed the study. The general clinical and demographic characteristics of the subjects are listed in Table 1. There were no significant difference between patients and controls with regard to either age or sex. The HY stages of the PD patients ranged from 1 to 2.5. The mean duration of motor symptoms in PD was 10 months.

The frequency and mean NMSS scores of specific non-motor symptom in patients and controls are shown in Table 2. All patients and 68% of controls reported at least 1 NMS. Significantly higher frequency of NMS in PD patients can be observed in cardiovascular, sleep/fatigue, mood/cognition, halucinations, attention/memory, others domains comparing to controls ($p < 0{,}001$ for each domain). There is no difference in frequency of GI, urinary and sexual symptoms comparing two groups. Most patients suffered from sleep/fatigue, mood/cognition and attention/memory non-motor difficulties (97.2%; 98.6%; 97.2%; respectively), while sleep/fatigue and urinary problems were the most expressed in controls (63.3%; 75%; respectively). Total NMSS score is higher in PD group compared with controls indicating that NMS are more serious and frequent among PD patients (median PD 38,00 vs. controls 8,00; $p < 0.001$). The highest NMSS score is present in mood/cognition domain in patients group (median 14.0) and in urinary domain in controls (median 3.0).

The relation of each domain's NMSS score to age, duration of motor symptoms, HY stage and UPDRS motor score is shown in Table 3. There was no significant correlation between age and specific domain scores in patients and controls. The scores of sleep/fatigue and attention/memory domains have positive correlation with the duration of motor symptoms ($p = 0.013$; $p = 0{,}004$; respectively). Strong correlation with HY score was observed in cardiovascular and mood/cognition domains ($p = 0.047$; $p = 0{,}017$; respectively). Greater motor difficulties expressed by the motor UPDRS score had positive impact on severity and frequency of cardiovascular, mood/cognition and urinary symptoms in PD patients ($p = 0.007$; $p < 0.001$; $p = 0.026$; respectively). Higher total NMSS score was associated with higher each domain score.

## 4. Discussion

The results of our cross-sectional study show that the prevalence and severity of non-motor symptoms are higher in PD group comparing to healthy control group. Studies on non-motor symptoms in early de novo PD subjects are lacking.

Grosset et al. have shown that patients with early PD left untreated soon after diagnosis deteriorated in motor but also in non-motor domains such as cognition, emotional well-being, and bodily discomfort, in contrast to patients in whom PD treatments were started early [18].

Chaudhury et al., have demonstrated that the most frequently nondeclarated symptoms were delusions, daytime sleepiness, intense and vivid dreams, and dizziness. Use of Non-Motor Symptoms Questionnaire (NMSQuest) allows patients to flag symptoms which may be otherwise undeclared [19].

Recently published data suggest that the presence of NMS should be included in clinical criteria for establishing the diagnosis of PD [8]. It is based on the evidence that PD reflects different parts of nervous system [20,21]. Additionally, early detection of clinical biomarkers of incipient PD may provide a future opportunity to intervene with neuroprotective agents. Some of NMS have already been recognized as predictors of PD, sometimes by many years: REM sleep behavior disorder (RBD) [22], constipation [23], orthostatic hypotension [24], urinary urge and erectile dysfunction [25,26], depression [27], daytime somnolence [6], hyposmia [28].

The majority of previously reported results include whole PD population from early to late disease stage. Longer disease duration and more severe stages are associated with more non-motor symptoms [3,29,30]. In addition to the evolution of NMS as an intrinsic part of the disease, treatments used in PD can trigger or worsen the symptoms. Some of these effects include orthostatic hypotension, daytime somnolence and sleep attacks, emotional and pain complaints that fluctuate in relation to L-dopa dosing, psychosis, the dopamine dysregulation syndrome (DSS) [31,32].

NMS in PD group differ from those in aged matched controls in frequency, severity and domain involvement. Mood/cognition, attention/memory and sleep/fatigue disturbances were the most frequent NMS in our PD patients and rarely seen in controls. Three most prevalent NMSs among de novo PD patients in another study were "nocturia", "forget things and events" and "restless legs" with more common attention/memory and gastrointestinal domains comparing to healthy controls [33]. Neuropsychiatric symptoms,