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Impact of pre-morbid depression on health-related quality of life in non-demented Parkinson's disease patients☆

Nataša Klepac [a], Sanja Hajnšek [a], Vladimir Trkulja [b,*]

[a] Department of Neurology, University Hospital Centre Zagreb, Zagreb University School of Medicine, Kišpatićeva 12, Zagreb, Croatia
[b] Department of Pharmacology, Zagreb University School of Medicine, Šalata 11, 10000 Zagreb, Croatia

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ABSTRACT

The need to understand and improve health-related quality of life (Hr-QoL) in Parkinson's disease (PD) has been emphasized. In order to investigate contributions of depression that existed before the onset of typical motor symptoms ("pre-PD depression"), idiopathic non-demented non-psychotic patients with ($n = 32$) and without ($n = 120$) a history of pre-PD depression, free of relevant comorbidity, calliper-matched for age, education and disease duration were evaluated for motor and non-motor disease aspects and Hr-QoL (Parkinson's Disease Questionnaire 39, PDQ-39). History of pre-PD depression was independently associated with higher actual levels of depression and anxiety, poorer sleep quality and mental set shifting, which all contributed to poorer Hr-QoL. Mediation analysis demonstrated significant indirect effects (mediated through the effects on mood/emotion/sleep and/or cognition) of pre-PD depression on PDQ summary index and subscales, but also direct (non-mediated) effects on emotional well-being and body discomfort subscales independent of the sociodemographic, motor/non-motor disease or treatment-related characteristics. Data indicate that for a given level of motor/non-motor PD symptoms severity, history of pre-PD depression contributes to poorer Hr-QoL.

1. Introduction

Health-related quality of life (Hr-QoL) is a self-perceived well-being related to or affected by a disease or its treatment [1]. Parkinson's disease (PD) is a progressive illness with both motor and non-motor symptoms [2] where Hr-QoL results from a complex interplay of these primary disease-related characteristics combined with treatment side effects [3]. The need to understand and improve the overall burden conferred by PD, subsumed within the Hr-QoL concept, has been emphasized over recent years [4]. In this respect, the role of depression (clinical diagnosis or level of difficulties assessed using measuring scales) has been repeatedly stressed [5–8]. Addressing this and other potentially treatable elements of Hr-QoL may bring benefits to both patients and community [4]. In this context, it appears reasonable to look for pre-morbid factors before their impact on Hr-QoL has developed, that may predict future quality of life and/or may guide preventive actions.

Several case-control or prospective cohort studies found that the risk of developing PD was higher among depressed subjects [9], but attempts to characterize other risk factors or "pre-morbid parkinsonian personality" have been limited [10]. Even less is known about "pre-PD" elements that would reflect on Hr-QoL once the disease has developed. Higher education levels have been shown to predict milder depressive difficulties at a given level of PD severity in non-demented patients and indirectly they also favour better Hr-QoL [11]. Here we hypothesize that a history of depression existing before the onset of motor symptoms leads to poorer Hr-QoL after PD has been diagnosed. Although dementia and psychosis are not infrequent in PD and influence Hr-QoL [2,4], our cohort consisted of non-demented, non-psychotic patients.

2. Patients and methods

2.1. Outline

Patients with (test) and without (control) a history of depression before symptom onset (pre-morbid or pre-PD depression) were included in this cross-sectional study. All subjects signed informed consent and the study was approved by the institution's ethics committee. Hr-QoL was considered a final endpoint determined mainly by the motor and non-motor disease characteristics. We first assessed whether pre-PD depression influenced disease features by comparing the two groups. We then evaluated the effects of disease characteristics on Hr-QoL and compared the two groups to assess effects of pre-PD depression.

2.2. Patients

The diagnosis of idiopathic PD was made using the UK Parkinson's Disease Society Brain Bank criteria [12] To confirm the diagnosis, they were examined

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* Corresponding author. Tel.: +385 1 45 66 83; fax: +385 1 49 200 49.
E-mail address: vtrkulja@mef.hr (V. Trkulja).

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twice and on both occasions, which were at least 6 months apart, the UK PDSBB criteria for idiopathic PD had to be met. We used a structured interview (patients, caregivers), medical history review, neurological and consultant assessments to identify test patients based on the following: 1) They had suffered from a major depression, dysthymia, minor depression or depressive episodes, in line with DSM-IV/ICD-10 criteria during the five years preceding diagnosis; 2) During this period, they had not received other psychiatric diagnoses and they had not received neuropsychiatric treatment other than that for PD and depression (occasional use of anxiolytics allowed); 3) At the time of the assessment (a) they were non-demented according to the DSM-IV criteria and had Mini Mental State Examination (MMSE) score equal to or higher than the median value determined in a reference population-based sample of corresponding age and education [13], (b) neurodegenerative diseases other than PD, cerebrovascular diseases or sequelae, psychosis or antipsychotic treatment were excluded, and (c) somatic diseases with a potential effect on mood, cognition and quality of life were excluded (e.g., pain syndromes, advanced diabetes mellitus, malignancy, renal, hepatic or heart failure, severe anemia, or any other acute or chronic debilitating or life-threatening disease/state). A total of 32 patients were identified. Controls were identified using the same criteria except that none of them had any psychiatric diagnosis/treatment (except occasional anxiolytics) during a 5-year period preceding the onset of motor symptoms. For each test patient at least three controls caliper matched for age (±4 years), length of formal education (±2 years) and PD duration (0.5–2 years, >2–6 years, >6–10 years, >10 years) were enrolled. A total of 128 patients (ratio 1:3) would have provided >80% power to detect an average between group difference in an outcome of 30% assuming relative standard deviation of 50% and two-sided alpha level 0.05. Ultimately 152 patients (120 controls) were enrolled.

2.3. Evaluations

Patients were screened during their regular visits and were scheduled for further assessments the following week. All evaluations were done during the "on" state. We used Unified Parkinson's Disease Rating Scale (UPDRS) part 3 and modified Hoehn and Yahr scoring (H&Y) to rate motor symptoms (higher scores = more severe symptoms), UPDRS part 2 to assess activities of daily living (ADLs) (higher score = poorer ADLs), Non-motor Symptoms Assessment Scale in PD (NMS) domains 1 (cardiovascular/falls), 6 (gastrointestinal), 7 (urinary), 8 (sexual function) and 9 (pain and sweating) to quantify severity of somatic non-motor symptoms (higher score = more severe symptoms) and domain 4 to detect perceptual problems/hallucinations. Neuropsychological evaluation addressed: 1) Daytime sleepiness (Epworth daytime sleepiness scale (ESS), higher score = more severe sleepiness); 2) Overall sleep quality {Pittsburgh Sleep Quality Index (PSQI), higher score = poorer quality}; 3) Level of depression {Beck's Depression Inventory (BDI), higher score = more severe depression}; 4) Level of anxiety {Hamilton Anxiety Rating Scale (HAM-A), higher score = more severe anxiety}; 5) Cognitive domains: (a) *Phonemic verbal fluency* assessed using the Controlled Word Association Test (COWAT) FAS with number of words starting with letter F, A and S produced within 1 min as a score [14]; (b) *Semantic verbal fluency* assessed using COWAT Plant with a number of plants named within 1 min as a score [14]; (c) *Visuoverbal substitution speed* (attention and scanning abilities) assessed using the Symbol Digit Modalities Test (SDMT) with number of correct number-symbol matches produced within 90 s as a score [15]; (d) *Mental set shifting/response inhibition* (relevant for executive functioning) assessed based on differences in scores in Trail Making Tests A and B (Δ Trails = Trail B − Trail A). In Trail A, patients draw a line connecting numbers in ascending order. In Trail B, patients draw a line connecting numbers with alternating letters in an ascending order (e.g., 1-A-2-B…). The score is time in seconds needed for the task. Δ Trails is a Trail B score "corrected" for the Trail A elements (attention, sequencing, information processing and motor speed) and is considered a measure of mental set shifting and response inhibition [16]. The higher the score the better for all tests except for Δ Trails. Cognitive tests were administered in a separate ≤60 min session, after a night's rest.

Parkinson's Disease Questionnaire 39 (PDQ-39) summary index (SI) and subscales were evaluated to assess health-related quality of life (Hr-QoL).

Antiparkinsonian and mood/emotion-affecting drugs were recorded. Patients were considered as "using antidepressants" if on an ongoing (≥2 weeks) treatment at the time of evaluation or if they had received systematic treatment that stopped within two weeks of the evaluation.

2.4. Statistics

Univariate tests were used for unadjusted and linear regression was used for adjusted comparisons and for this purpose some of the data had to be transformed. Principal components analysis (varimax rotation, Kaiser normalization, eigenvalue > 1.0 as a component-forming criterion) was performed to assess "grouping" of variables describing motor and non-motor PD aspects. To assess potential indirect effects of presumed predictors on outcomes, multiple mediator models with covariates were analyzed as described by Preacher and Hayes [17]. We used SAS for Windows 9.1.3 (SAS Inc., Cary, NC, USA) software.

3. Results

3.1. Descriptives and unadjusted comparisons between groups

Patients with (test) and without (control) a history of pre-PD depression were comparable regarding sociodemographics (Table 1). History of motor PD symptoms was somewhat longer in the control group ($P = 0.022$) (Table 1). Almost all test patients (81.3%) were using antidepressants vs. a minority of the controls (14.2%) (Table 1). All "users" were taking treatment >2 months, whereas "non-users" had never taken antidepressants. Other treatments were comparable for the two groups (Table 1).

Only a few patients (<5%) in either group scored >0 on the NMS domain 4 (perceptual problems/hallucinations). This item was not analyzed further. Actual levels of depression ($P = 0.001$) and anxiety ($P = 0.003$) were higher and sleep quality appeared somewhat worse ($P = 0.093$) in the test group. Other motor and non-motor PD aspects were comparable for the two groups (Table 2). Test patients scored worse than controls on the emotional well-being PDQ-39 subscale ($P < 0.001$). No apparent differences were observed regarding PDQ-SI and other subscales (Table 2).

3.2. Effect of pre-PD depression on motor and non-motor PD aspects: adjusted comparisons between groups

Testing for independent associations between history of pre-PD depression and PD aspects (motor or non-motor), adjusted analyses accounted for calliper-matching (age, education, PD duration) and other relevant covariates. For each outcome, a regression model was first built by a stepwise procedure and then history of pre-PD depression (to compare the two groups) and calliper-matching variables were forced into the model – if not already included. Patient and disease-related characteristics (Tables 1 and 2) (except for Hr-QoL-measuring variables) were considered as potential covariates. To avoid aliasing and co-linearity, we first conducted principal components analysis (PCA) involving motor and non-motor PD characteristics to evaluate their multivariate associations. Epworth scale (communality < 0.5) and NMS somatic (loaded onto two components with similar loadings) were excluded from PCA. Three components were identified: 1) "Cognition" (cognitive tests; loadings between 0.662 and 0.804); 2) "Mood/emotion and sleep" (BDI, HAM-A, PSQI; loadings between 0.758 and 0.853); 3) "Motor symptoms and physical ALDs" (UPDRS 3, H&Y and UPDRS 2; loadings between 0.725 and 0.800). Consequently, selection lists of potential covariates were defined as follows: 1) For a particular cognitive test as an outcome, other cognitive tests were omitted; 2) For "mood/emotion & sleep" variables as outcomes, variables loading onto the same component and cognitive tests (based on a premise that *mood* affects *cognition*) were omitted; 3) For ESS and NMS somatic, cognitive tests were omitted; 4) For UPDRS part 2, no variable was omitted; 5) For UPDRS part 3 and H&Y, demographics, disease onset and treatment characteristics were considered as potential covariates.

Of the analyzed outcomes, independent association with the history of pre-PD depression was found for higher actual depression (BDI), higher actual anxiety (HAM-A), poorer sleep quality (PSQI) and poorer mental set shifting/response inhibition (Δ Trails) (Table 3). History of pre-PD depression was selected into each of these models through a stepwise procedure. Use of antidepressants was not selected into models analyzing BDI, HAM-A or PSQI, and for several reasons we did not force it into these models. First, antidepressants were administered *due* to mood disturbances and it appeared implausible to view use of antidepressants as a covariate in the analysis of these outcomes. Second, there was almost a complete overlap between test patients and "antidepressant