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Apathy, fatigue and quality of life in patients with Parkinson's disease

Skorvanek, Matej

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Data sources, measures and statistical analyses

2.1 Sample and procedure

Patients were recruited from the Movement Disorders Units in Kosice, Bratislava and Martin as well as from 24 other neurology outpatient clinics in the eastern Slovakia region during the official validation of the Slovak translations of the MDS-UPDRS (1) and the Unified Dyskinesia Rating Scale (UDysRS) (2) in the period June 2011 – May 2014. Patients enrolled from the non-specialized neurology outpatient clinics were all examined by a single neurologist specialized in Movement Disorders (MS). Out of the core study sample of 354 patients examined during the MDS-UPDRS validation (Chapter 3), 252 patients examined in Kosice were eligible for the broader study. The inclusion criteria were a diagnosis of PD according to the UK PD Society Brain Bank Criteria (3) and normal cognitive status as assessed with the Mini-Mental State Examination (>24 points) (4). Patients with lower MMSE scores (N=24) and those who initially agreed to participate in the additional study but did not fill in the questionnaires or whose data were partially missing (N=38) were excluded. In addition, patients with atypical forms of parkinsonism were a priori excluded from the study. A total of 190 non-demented patients (75.4%) remained for the analysis (Chapters 5, 6, 7). During the validation of the Slovak version of the UDysRS an additional sample of 113 non-demented patients from Bratislava, Martin and Kosice were added to the final sample of 304 PD patients (Chapter 4).

One week before the interview an invitation letter, a written informed consent form and questions on sociodemographic background, medical history, current medication and self-report questionnaires (described below) were sent by postal mail to patients diagnosed with PD. During the interview, a trained interviewer assessed the cognitive functioning of patients using the MMSE and reviewed the questionnaires together with the patient to ensure that no values were missing. Afterward, a neurologist specialized in Movement Disorders assessed each patient's disease severity using the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (1), including Hoehn and Yahr staging (5). Patients who were unable to fill in the questionnaires by themselves due to motor impairment answered identical questions

during the oral interview. The study was approved by the respective Local Ethics Committees. All patients participated voluntarily and gave written informed consent prior to the interview. The investigation was performed according to the Declaration of Helsinki.

2.2 Measures

2.2.1 Sociodemographic data

Sociodemographic data included age, gender, length of education in years and education level. Education level was classified as: low (primary school or unfinished high school), middle (finished high school or specialization after high school – not a college or university) or high (university undergraduate or postgraduate or higher academic degree achieved).

2.2.2 Questionnaire data

Quality of life (QoL)

QoL was assessed using the Parkinson's Disease Quality of Life Questionnaire (PDQ-39) (6). It is a disease-specific self-administered questionnaire comprised of 39 questions, each of them using a five-point ordinal scoring system, from which a single summary index can be calculated. For the summary index the scores were standardized from 0 to 100, so that higher scores indicate poorer QoL. The PDQ-39 measures 8 dimensions of health-related QoL: mobility, activities of daily living (ADL), emotional well-being, stigma, social support, cognition, communication and bodily discomfort. The PDQ-39 has been shown to be feasible, reliable, valid, and responsive to change in patients with PD and to have good internal consistency (7). Cronbach's alpha for the total PDQ39 in our study (Chapters 4 and 6) was 0.96.

Fatigue

Fatigue was assessed with the 20-item self-report Multidimensional Fatigue Inventory (MFI) (8), which measures five dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. Each subscale contains four items, which are scored on a five-point Likert-scale. The negative formulated items must be recoded before totaling the scores. Scores range from 4 (absence of fatigue) to 20 (maximum fatigue) for each subscale. A recent study found the MFI to be reliable and valid for the assessment of fatigue in patients with PD (9). We used a uniform cutoff score of ≥ 13 in each MFI domain to define the presence of fatigue. This was in accordance with a previously published MFI general fatigue domain cutoff score of ≥ 13 for defining severe fatigue in chronic fatigue syndrome (10). Cronbach's alpha for the MFI in this study was 0.89 (Chapters 5, 7)

Depression and anxiety

The Beck Depression Inventory-II (BDI-II) is a self-administered 21-item scale assessing depression (11). Each answer was scored as 0-3. The cutoff values used are 0-13: normal range; 14-19: mild depression; 20-28: moderate depression; and 29-63: severe depression (11). Higher total scores indicate more severe depressive symptoms. Cronbach's alpha for BDI-II in our study was 0.90 (Chapters 5, 6, 7).

The Hospital Anxiety and Depression Scale (HADS) is a self-administered scale with two subscales capable of evaluating anxiety (HADS-A) and depression (HADS-D) (12). This 14-item scale consists of seven items assessing anxiety and seven items assessing depression, with scoring from 0 (no problem) to 3 (extreme problem). The cutoff values applied are ≤ 7 on each subscale: unimpaired; 8-10 on each subscale: possibly impaired; and ≥ 11 on each subscale: probably impaired (12). In the present study, we found Cronbach's alpha to be 0.83 for the anxiety domain and 0.82 for the depression domain (Chapter 6).

Sleep

Excessive daytime somnolence (EDS) was evaluated with the Epworth Sleepiness Scale (ESS) (13). ESS measures dozing behaviour in eight different situations. This self-assessment questionnaire asks the respondent to rate the likelihood of falling asleep on a scale from 0 to 3. The total ESS score is the sum of all the responses and ranges from 0 to 24; higher scores reflect greater sleep propensity. Consistent with a number of previous investigations, a score of 10 as the cutoff point was used for normal, while scores above this imply pathological sleepiness (14). Cronbach's alpha for the ESS was 0.84 (Chapter 7).

The Pittsburgh Sleep Quality Index (PSQI) (15) was used to assess nighttime sleeping problems. The PSQI assesses global sleep quality and disturbances in sleep patterns during the previous month in seven components. After recoding, each component has possible scores of 0-3, where 3 indicates the negative extreme. The global PSQI score is the sum of all component scores (range 0-21); a score of ≥ 5 indicates a poor sleeper. Cronbach's alpha for the PSQI was 0.85 (Chapter 5).

Apathy

Apathy was evaluated using the Starkstein Apathy Scale, which is a self-administered 14-item scale for assessing apathy (16). Each answer is scored from 0 (not at all) to 3 (a lot), with a higher summary score meaning more apathy. A cutoff of ≥ 14 is used to define the presence of apathy. In the present study, Cronbach's alpha was 0.78 (Chapters 6, 7).

2.2.3 Medication and disease related data

Information on disease duration, age at disease onset, antiparkinsonian

medication and other treatment was obtained during the interview. The levodopa equivalent daily dosage (LEDD) was calculated using a previously published formula (17). Motor symptoms were rated in the ON state using the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (motor examination). The MDS-UPDRS is a four-subscale combined scale (non-motor experiences of daily living - nmEDL, motor experiences of daily living - mEDL, motor examination - MEX and motor complications - MCompl) (1). MDS-UPDRS part I (nmEDL) comprises 13 items. Six of these items – Cognitive impairment, Hallucinations and psychosis, Depressed mood, Anxious mood, Apathy and Features of dopamine dysregulation syndrome (DDS) – are assessed via a semi-structured interview and seven items – Sleep problems, Daytime sleepiness, Pain and other sensations, Urinary problems, Constipation problems, Light-headedness on standing and Fatigue – are assessed through a self-report questionnaire. MDS-UPDRS part II (mEDL) is composed of 13 items which are assessed in the form of a self-report questionnaire. MDS-UPDRS part III (MEX) comprises 33 scores based on 18 items and is performed as a physical evaluation of the patient. MDS-UPDRS part IV (MCompl) includes six items assessed via a semi-structured interview. Items are scored on a five-point scale, ranging from 0 (normal) to 4 (severe), and they are then summed for the total score of each scale section. The disease stage was assessed by the Hoehn & Yahr scale (HY), which is applied to gauge the course of the disease over time (5).

2.3 Statistical analyses

Statistical analyses were performed using the statistical software program PASW SPSS version 18.0 (Chapters 5, 6, 7) and version 20.0 (Chapter 4) for Windows (SPSS Inc, Chicago IL); the statistical software M-plus version 6.11 was also used (Chapter 3). First, the demographic and clinical characteristics of the studied samples were described. Significant differences between the studied group characteristics (Chapters 5, 6, 7) were analysed by independent sample t-tests and chi-square tests. Statistical differences regarding the coincidence of fatigue in different domains and apathy in both depressed and non-depressed patients were tested using the Fisher's Exact Test (Chapter 7). Separate multiple linear regression analyses were performed in order to study the relationship between the studied variables (Chapters 4, 5, 6, 7). In terms of validation of the Slovak translation of the MDS-UPDRS, a confirmatory factor analysis (CFA) was conducted as the primary outcome to determine if the factor structure for the English language MDS-UPDRS (Goetz et al., 2008) could be confirmed in data collected using the Slovak translation. As a secondary analysis an exploratory factor analysis for the Slovak version of MDS-UPDRS Parts I-IV using an unweighted least squares (ULS) approach was conducted

to explore the underlying factor structure without the constraint of a pre-specified factor structure (Chapter 3).

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