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Relationship between the non-motor items of the MDS–UPDRS and Quality of Life in patients with Parkinson's disease

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ABSTRACT

The Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS–UPDRS) is a newly developed comprehensive tool to assess Parkinson's disease (PD), which covers a wider range of non-motor PD manifestations than the original UPDRS scale. The aim of this study was to assess the relationship between the MDS–UPDRS and Quality of Life (QoL) and to analyze the relationship between individual MDS–UPDRS non-motor items and QoL.

A total of 291 PD patients were examined in a multicenter Slovak study. Patients were assessed by the MDS–UPDRS, HY scale and PDQ39. Data were analyzed using the multiple regression analyses.

The mean participant age was 68.0 ± 9.0 years, 53.5% were men, mean disease duration was 8.3 ± 5.3 years and mean HY was 2.7 ± 1.0. In a multiple regression analysis model the PDQ39 summary index was related to MDS–UPDRS parts II, I and IV respectively, but not to part III. Individual MDS–UPDRS non-motor items related to the PDQ39 summary index in the summary group and in the non-fluctuating patients subgroup were pain, fatigue and features of dopamine dysregulation syndrome (DDS). In the fluctuating PD patient subgroup, PDQ39 was related to pain and Depressed mood items. Other MDS–UPDRS non-motor items e.g. Anxious mood, Apathy, Cognitive impairment, Hallucinations and psychosis, Sleep problems, Daytime sleepiness and Urinary problems were related to some PDQ39 domains.

The overall burden of NMS in PD is more important in terms of QoL than motor symptoms. Individual MDS–UPDRS non-motor items related to worse QoL are especially pain and other sensations, fatigue and features of DDS.

1. Introduction

The Unified Parkinson's Disease Rating Scale (UPDRS) [1] has been historically the most commonly used tool for a comprehensive assessment of Parkinson's disease. The Movement Disorder Society (MDS) sponsored revision of the UPDRS — the MDS–UPDRS has been published in 2008 [2]. The MDS–UPDRS is composed similarly as the original scale from four parts – non-motor and motor experiences of daily living (part I and II), motor examination (part III) and motor complications (part IV). The main aim of this revision was to address the shortages of the original scale, to improve scale properties and cover a bigger number of PD manifestations particularly including some non-motor symptoms (NMS), which were not part of the original scale. The MDS–UPDRS has demonstrated good reliability and validity also in multiple other studies [3–5].

The MDS–UPDRS covers areas which have been all previously associated with worse Quality of Life (QoL) in PD patients, however pilot results from a part of our cohort [6] as well as a subsequent study of Martinez-Martin et al. [7] have shown that the MDS–UPDRS components significantly related to worse QoL were the subscores of non-motor experiences of daily living (nmEDL) and motor experiences of daily living (mEDL), whereas the motor examination (MEx) as well as the motor complications (MCompl) subscores were not significantly related to worse QoL. The importance of NMS regarding QoL has been shown in multiple previous studies, where the NMS, including

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mood and sleep disorders, Apathy, fatigue, dysautonomia, pain and Hallucinations, had a bigger impact on QoL than the motor symptoms examined by the original UPDRS part III [8–11]. In a previous study validating MDS–UPDRS part I (nmEDL), all individual items except Cognitive impairment, despite their brevity, had a significant correlation with other validated instruments used to assess NMS in PD [12], making the MDS–UPDRS part I an easy and practical tool to assess the burden of NMS in PD. Despite the known correlation between the overall burden of NMS and worse QoL in PD, the impact of individual non-motor items of the MDS–UPDRS on QoL has not been studied so far. Moreover, different NMS can occur as a consequence of antiparkinsonian therapy and be related to motor and non-motor fluctuations.

Therefore, the aim of the present study was to analyze the relationship between the MDS–UPDRS domains and QoL, and further to analyze the impact of the individual MDS–UPDRS non-motor items on QoL and its different domains in the summary patient group, as well as separately for the non-fluctuating and fluctuating patient subgroups.

2. Materials & methods

2.1. Design

The study was a national Slovak, multicenter, cross-sectional evaluation study.

2.2. Patients

Patients were recruited from 3 major Slovak Movement Disorder Centers from the whole region of Slovakia between June 2011 and May 2014 during the validation projects of the Slovak versions of the MDS–UPDRS [2] and the Unified Dyskinesia Rating Scale (UDysRS). All patients were diagnosed according to the UK PD Society Brain Bank Criteria [13], and their mental abilities were assessed with the Mini-Mental State Examination (MMSE) [14]. All patients with atypical forms of Parkinsonism were excluded from the study. A total of 323 patients initially agreed to participate in the study. Patients with an MMSE score lower than 24 (N = 18) and those whose data were partially missing (N = 14) were excluded. A total of 291 non-demented patients (90%) remained for analysis.

2.3. Data collection

On the day of the examination a trained interviewer assessed the cognitive functioning of patients using the MMSE and a neurologist specialized in Movement Disorders (MS, MG, MM, VH and PV) assessed each patient's disease severity using the MDS–UPDRS [2], including Hoehn and Yahr staging [15]. Subsequently, the patients received questionnaires comprising questions on their sociodemographic background, medical history, current medication and self-report questionnaires (described below), which were filled in within a week from the examination and were later reviewed by the clinician together with the patient to ensure that no values were missing. Patients who were unable to fill in the questionnaires by themselves due to motor impairment answered the identical questions during the oral interview. The study was approved by the Local Ethics Committees. All patients participated voluntarily and gave written informed consent prior to the study. The investigation was performed according to the Declaration of Helsinki.

2.4. Measures

Sociodemographic data, including age, gender and education, were obtained from the structured interview. 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).

2.4.1. Disease and medication-related data

Information on disease duration, antiparkinsonian medication and other treatment was obtained during the interview. The levodopa equivalent daily dosage (LEDD) was calculated using a previously published formula [16]. Motor symptoms were rated in the ON state using the 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) [2]. This instrument was recently translated into Slovak and approved as an official non-English translation of the MDS–UPDRS [3]. 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 a 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 [15].

2.4.2. Quality of Life (QoL)

QoL was assessed using the Parkinson's Disease Quality of Life Questionnaire (PDQ-39) [17]. 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 [18]. The Cronbach's alpha for PDQ39 in our study was 0.96.

2.5. Statistical analyses

Statistical analyses were performed using the statistical software program PASW SPSS version 20.0 for Windows (SPSS Inc., Chicago IL). First, we described the demographic and clinical characteristics of our study group. Subsequently, multiple linear regression analysis was performed in order to study the relationship of sociodemographic factors, disease duration, and different MDS–UPDRS subscales on QoL. Finally, separate multiple regression analyses were performed in order to study the relationship between the individual MDS–UPDRS non-motor items and QoL controlled for sociodemographic factors, disease duration and MDS–UPDRS part III (MEx) in the summary group as well as separately for non-fluctuating and fluctuating patient subgroups.

3. Results

The mean age of the PD sample was 68.0 ± 9.0 years; 53.5% were men, the mean disease duration was 8.3 ± 5.3 years, and the mean HY stage was 2.7 ± 1.0 (72% stage II–III). Motor fluctuations were present in 205 patients (70.5%) and dyskinesias in 122 patients (42%),

while 82 patients (29.5%) had no motor fluctuations. Baseline characteristics of the study population can be found in Table 1.

In a multiple regression analysis model worse Quality of Life measured by the PDQ39 summary index was significantly related to the MDS–UPDRS part I (nmEDL), part II (mEDL) and part IV (MCompl) respectively, however it was not related to the MDS–UPDRS part III (MEx) or other socio-demographic factors evaluated (Table 2).

3.1. Determinants of QoL in a model with individual MDS–UPDRS non-motor items

Worse Quality of Life measured by the PDQ39 summary index was associated with the MDS–UPDRS items pain and other sensations, fatigue and features of DDS as well as with longer disease duration and higher MDS–UPDRS part III (MEx) scores. The same variables were related to the PDQ39 Activities of daily living subscore and also to PDQ39 mobility subscore, which was related also to female gender. PDQ39 Emotional well-being was related to the items Depressive mood, pain, Sleep problems and Anxious mood respectively. PDQ39 stigma was related to younger age and the items Depressive mood, Apathy, features of DDS and Urinary problems. PDQ39 social support was related to the items Hallucinations and psychosis and features of DDS. PDQ39 cognition was related to older age and the items Daytime sleepiness, Hallucinations and psychosis, Cognition, fatigue and Anxious mood respectively. PDQ39 communication was related to the items features of DDS and Anxious mood as well as to longer disease duration and MDS–UPDRS part III (MEx). PDQ39 bodily discomfort was related to the items pain and other sensations, Urinary problems and female gender respectively. MDS–UPDRS items Constipation problems and Light headedness on standing were not related to any of the PDQ39 domains (Table 3).

3.2. Determinants of QoL in a model with individual MDS–UPDRS non-motor items in non-fluctuating vs. fluctuating patients

In a model with non-fluctuating PD patients worse Quality of Life was associated only with lower education level and with non-motor items fatigue, pain and other sensations and features of DDS, it was not related to motor status measured by the MDS–UPDRS III or disease duration. Disease duration or motor status was also not related to any PDQ39 subdomain in this subgroup of non-fluctuating patients (results not shown). On the other hand, in fluctuating PD patients, worse Quality of Life was related to longer disease duration, higher MDS–UPDRS III scores and non-motor items pain and other sensations and Depressed mood (Table 4).

Table 1
Characteristics of the study population (N = 291).

	Mean	SD	Median	Range
Age	68.0	9.0	70	30–88
Age at symptom onset	59.6	10.8	61	20–83
Gender (male/female)	156/135			
Education				
Low	117 (40%)			
Middle	120 (41%)			
High	54 (19%)			
Disease duration	8.3	5.3	7.0	0–30
Hoehn &Yahr stage	2.7	1.0	3.0	0–5
PDQ39 mobility	44.9	29.1	45.0	0–100
PDQ39 ADL	41.4	28.7	41.7	0–100
PDQ39 emotional well being	37.7	21.8	37.5	0–92
PDQ39 stigma	40.7	33.1	37.5	0–100
PDQ39 social support	14.5	17.5	8.3	0–75
PDQ39 cognition	29.7	20.4	25.0	0–88
PDQ39 communication	21.5	21.0	16.7	0–92
PDQ39 bodily discomfort	46.4	23.1	50.0	0–100
PDQ39 summary index	36.7	19.7	37.2	0–85
MDS–UPDRS part I	14.0	7.6	13	2–40
MDS–UPDRS part II	16.1	9.7	15	0–44
MDS–UPDRS part III	39.1	16.6	37	8–88
MDS–UPDRS part IV	5.6	5.4	5	0–22
Motor fluctuations (N)				
No fluctuation	82 (29.5%)			
Any motor fluctuations	205 (70.5%)			
Dyskinesias	122 (42%)			

PDQ39 – Parkinson's Disease Quality of Life Questionnaire-39, ADL – Activities of Daily Living, MDS–UPDRS – Movement Disorder Society–Unified Parkinson's Disease Rating Scale.

Table 2
Multiple linear regression: relationship between the MDS–UPDRS subscales and Quality of Life (PDQ39 summary index).

	β	Significance
Age	−0.05	P = ns
Male gender	−0.06	P = ns
Education level	−0.06	P = ns
Disease duration	−0.00	P = ns
MDS–UPDRS part I	0.30	P < 0.001
MDS–UPDRS part II	0.54	P < 0.001
MDS–UPDRS part III	0.00	P = ns
MDS–UPDRS part IV	0.12	P < 0.01
Adjusted R Square	0.78	

MDS–UPDRS – Movement Disorder Society–Unified Parkinson's Disease Rating Scale, PDQ39 – Parkinson's Disease Quality of Life Questionnaire-39.

4. Discussion

To our best knowledge, this is the first study to assess the relationship between individual non-motor MDS–UPDRS items and different domains of Quality of Life in PD patients. As shown in our and some previous studies [7–10], the overall burden of NMS in PD is more important with regard to QoL than motor symptoms. Symptoms related to worse QoL in our study were especially pain, fatigue and features of DDS and this relationship was found especially in patients without motor fluctuations, where only NMS and lower education level, not motor status or disease duration, were associated with worse quality of life. On the other hand, Quality of Life in fluctuating PD patients was determined by longer disease duration, worse motor status, higher depression and pain MDS–UPDRS scores. Other NMS symptoms such as Anxiety, Apathy, Cognitive impairment, Hallucinations, Sleep problems, Daytime sleepiness and Urinary problems were also related to some aspects of QoL.

Pain can be present in over 80% of patients with PD [19] and it has been repeatedly associated with worse Quality of Life [8,9,20], although not all studies found a significant difference in the association between pain and QoL when comparing PD patients and matched controls [21]. Pain in PD may be categorized into a number of different subtypes including musculoskeletal, dystonic, radicular neuropathies and central pain [19]. Our results highlighting the importance of pain in terms of worse QoL are in line with most of the previous reports [8,9,20]. Moreover, chronic pain is often associated with depression, which may further worsen the QoL of PD patients [20]. As found in our study, pain was related to worse Quality of Life in both fluctuating and non-fluctuating patients.

Our results showing a significant relationship of fatigue with worse QoL are in line with most of the previous studies in this regard [8,9,11,22]. Fatigue can also be present in up to 80% of PD patients [23] and the PRIAMO study found fatigue to be the most frequent of all NMS in 1072 consecutive PD patients [24], moreover fatigue is often perceived by PD patients as one of their most relevant problems [25]. As found in our study, fatigue was strongly related to worse Quality of Life especially in patients without motor fluctuations. This is in line with some previous reports showing a high prevalence of fatigue already in early or even premotor stages of PD [26]. Fatigue in PD can be divided into 'peripheral fatigue', which refers to an objectively measurable process in which a muscle loses strength after repeated contractions, and 'central fatigue', which refers to a feeling-state, perception or

Table 3
Multiple linear regression analyses: relationship between separate non-motor items of the MDS–UPDRS part I and HRQoL and its domains in a summary model.

	PDQ39 total	PDQ39 mobility	PDQ39 ADL	PDQ39 Emotional well being	PDQ39 stigma	PDQ39 social support	PDQ39 cognition	PDQ39 communication	PDQ39 bodily discomfort
Age	−.11	−.08	−.08	−.08	−.30***	−.13	.15*	−.09	.08
Male gender	−.03	−.13*	.08	−.08	−.03	−.08	.14*	18**	−.09
Education	−.03	−.04	−.05	−.01	.06	.08	−.10	−.02	−.08
Disease duration	.14**	.22***	.23***	−.08	.10	−.06	−.06	.18**	.05
MDS−UPDRS III	.13**	.20***	.27***	.01	.08	−.13	.01	.14*	−.05
Cognition	.06	.04	.03	−.01	.06	.11	.15*	−.02	.02
Hallucinations	.03	−.00	−.01	.07	.05	.16*	.15*	.07	−.09
Depression	.10	−.05	.07	.19**	.23**	.10	.08	−.02	.04
Anxiety	.04	−.03	−.02	.15**	−.05	.03	.15*	.17*	.10
Apathy	.08	.07	.02	.12	.17*	−.23	−.01	.11	−.12
Features of DDS	.10*	.10*	.16**	.03	.14*	.13*	−.02	.15*	−.06
Sleep problems	.05	.06	−.01	.19**	−.10	.02	.07	.06	.12
Daytime sleepiness	.02	−.02	−.03	.03	−.04	.10	.30***	.05	.11
Pain	.25***	.29***	.18**	.18***	.06	.11	.08	.07	.50***
Urinary problems	.05	.05	.05	−.02	.15*	.05	.00	.08	.20**
Constipation	.06	.05	.03	.10	.02	.07	.00	−.03	.03
Light headedness	.10	.10	.07	.13*	.05	.07	.02	.05	.13
Fatigue	.18**	.13*	.20**	.10	.09	.05	.15*	.09	−.03
Adj. R square	0.65	0.58	0.58	0.58	0.44	0.16	0.46	0.38	0.36

All analyses controlled for age, gender, education level, disease duration, MDS−UPDRS part III (motor examination) and all individual items of the MDS−UPDRS part I (nmEDL).
MDS−UPDRS – Movement Disorder Society–Unified Parkinson's Disease Rating Scale, PDQ39 – Parkinson's Disease Quality of Life Questionnaire-39.
Values represent beta coefficients.
* P < 0.05.
** P < 0.01.
*** P < 0.001.

experience that is not yet objectively measurable and which can be further divided into physical and mental fatigue domains [23]. Furthermore, according to the presence or absence of confounding factors - depression and Daytime sleepiness, fatigue can be divided into “primary” and “secondary” fatigue [23].

The significant relationship of features of DDS to worse QoL found in our study is supported by some studies which also found a significant link in this regard [27,28]. Impulsive and compulsive behaviors in PD are most commonly linked to dopaminergic drugs, especially dopamine agonists, but also L-dopa, and their prevalence in treated PD patients has been estimated around 14% [29]. These behaviors encompass impulse control disorder, punding and the dopamine dysregulation syndrome, which refers to the compulsive use of dopaminergic medications well beyond the dose needed to optimally control motor disability [28]. Despite their relatively low prevalence, the presence of these behavioral issues may result into severe problems in patient's personal and family life.

Table 4
Multiple linear regression analyses: relationship between separate non-motor items of the MDS–UPDRS part I and HRQoL in patients with or without motor fluctuations.

	PDQ39 total patients without fluctuations	PDQ39 total patients with fluctuations
Age	.02	−.06
Male gender	−.07	.03
Education	−.19**	.03
Disease duration	−.05	.26***
MDS–UPDRS III	−.02	.1*
Cognition	.11	.08
Hallucinations	.08	−.01
Depression	.13	.17*
Anxiety	−.10	.09
Apathy	.04	.07
Features of DDS	.16*	.04
Sleep problems	.11	.12
Daytime sleepiness	.11	−.05
Pain	.24**	.18*
Urinary problems	−.03	.11
Constipation	.13	−.02
Light headedness	.04	.15
Fatigue	.40***	.07
Adj. R square	0.67	0.63

All analyses controlled for age, gender, education level, disease duration, MDS–UPDRS part III (motor examination) and all individual items of the MDS–UPDRS part I (nmEDL).
MDS–UPDRS – Movement Disorder Society–Unified Parkinson's Disease Rating Scale, PDQ39 – Parkinson's Disease Quality of Life Questionnaire-39.
Values represent beta coefficients.
* P < 0.05.
** P < 0.01.
*** P < 0.001.

Interestingly, despite previous reports, where depression has been a very consistent and significant determinant of worse QoL [8,9,22], the MDS–UPDRS item Depressed mood has not been significantly associated with the PDQ39 summary index score in our summary model or in the non-fluctuating patients subgroup, but only in fluctuating patients subgroup. However, depression remains a significant contributor to worse QoL as it is often associated with pain [19], fatigue [23], impulse control disorders [28], as well as other NMS in PD.

In contrast with the previous study of Martinez-Martin et al. [7], where worse QoL was significantly related to MDS–UPDRS part I (nmEDL) and part II (mEDL) only, in our study we found a significant relationship also with the MDS–UPDRS part IV (MCompl). This difference might be potentially explained by a higher prevalence of both motor fluctuations and dyskinesias in our study sample. Motor fluctuations may carry with them severe co-morbidity, they can be socially embarrassing and may prevent or impede the daily activities of PD patients [29]. Our results are in line with some other studies showing a significant relationship between the presence of motor complications and worse QoL in PD [30,31].

4.1. Strenghts and limitations

To the best of our knowledge, this is the first study to specifically correlate individual MDS–UPDRS non-motor items with QoL and its different domains. A large, multicenter sample including patients in all stages of the disease from the initial to the very late stages, as well as the use of validated and reliable measures present the strengths of this study. There are some limitations of our study. The sample consisted of more motivated patients who agreed to participate in the study and who were able to attend the examination. The cross-sectional design of the study does not allow us to further explore the causal pathways between the studied variables. Also, the absence of

demented patients in our sample does not allow us to generalize the results to the whole PD population.

4.2. Conclusions and implications for future studies and clinical practice

The overall burden of NMS in PD is a more significant contributor to the overall QoL than motor symptoms. Specific MDS–UPDRS non-motor items correlated with worse QoL in our summary model and in non-fluctuating patients were especially pain and other sensations, fatigue and features of DDS. In the fluctuating PD patients' subgroup NMS related to worse QoL were pain and Depressed mood. However, other symptoms including anxiety, Apathy, cognition, Hallucinations, sleep disorders and Urinary problems also contribute to certain aspects of QoL. The prevalence of NMS and their relationship to QoL changes throughout the disease course and therefore they should be actively screened and managed in order to improve patient's QoL. The MDS–UPDRS is a practical and comprehensive scale designed to cover the most important aspects of PD manifestations and to be the reference measure in future PD research. Therefore understanding the relationship between the MDS–UPDRS scale and QoL, which is an important concept in PD, has very relevant implications for both research, as well as clinical practice.

Conflict of interest and sources of funding statement

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