Relationship between the MDS-UPDRS and Quality of Life: a large international multicenter study of 3206 patients

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Abstract (250 words, limit 250)

Background

The relationship between Health-Related Quality of Life (HRQoL) and MDS-UPDRS has not been fully studied so far. The aim of this study was to evaluate the relationship between all MDS-UPDRS components and HRQoL in a representative international cohort of PD patients.

Methods

We collected demographic and disease-related data as well as MDS-UPDRS and PDQ8 scales. Data were analyzed using two hierarchical multiple regressions, first between the MDS-UPDRS Parts scores and PDQ8 and second between individual items from those Parts demonstrating significant relationship to PDQ8 in the first regression. LASSO regression analyses were performed to evaluate the relationship between PDQ8 and all individual MDS-UPDRS items.

Results

A total of 3206 PD patients were included in the study. In the first regression analysis PDQ8 was significantly related to MDS-UPDRS parts I and II, but not III and IV. In the second regression model significant contributions to PDQ8 were found for Part I items Fatigue, Pain, Depressed mood, Apathy; and Part II items Dressing, Doing hobbies, Freezing, Speech and Tremor. In the LASSO analysis, five Part I, six Part II, three Part III and one Part IV items contributed to PDQ8 scores. Five items most significantly related to the model were Depressed mood, Dressing, Apathy, Pain and Fatigue.

Conclusions

This is so far the largest study related to HRQoL issues in PD. Restrictions in activities of daily living and non-motor symptoms significantly contribute to QoL in PD.

Introduction
Health-related quality of life (HRQoL) has become one of the most important concepts and outcome measures for research as well as management of chronic conditions such as Parkinson’s disease (PD) (Martinez-Martin 2017). PD is a complex progressive multiorgan disorder affecting different neurotransmitter systems across central, peripheral and autonomic nervous system, thus resulting in a number of typical motor, but also non-motor symptoms, as well as motor and non-motor fluctuations and other complications later on in the disease course (Jellinger 2012). While historically motor symptoms were identified as the most relevant manifestations of the disease, recent studies demonstrated, that non-motor symptoms (NMS) and other aspects of the disease such as activities of daily living (ADL) may have a more significant impact on HRQoL than the motor symptoms (Martinez-Martín 2011, Skorvanek 2015a, Kadastik-Eerme 2015). Since HRQoL is a subjective, individual and multidimensional construct (Martinez-Martin 2017) its assessment may be influenced by many factors such as composition of the patient cohort in terms of disease severity, disease subtypes, social background, cultural and many other aspects. Tools which are used for this kind of analyses are also crucial to cover the most relevant aspects of PD. In this regard, the Movement Disorder Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) seems to be an easy and practical tool for such type of assessments since it covers most relevant clinical aspects of the disease including different NMS, ADLs, motor symptoms and motor fluctuations (Goetz 2008).

The aim of this study was to evaluate the relationship between all the MDS-UPDRS components and HRQoL in a large international cohort of PD patients representative of different disease subtypes, stages of the disease, cultural and language settings.

**Methods**

**Design**

This is an observational, cross-sectional, multicenter international study.

**Patients**
The study dataset consists of patients included in the QUAlity of Life in Parkinson’s Disease cohort (QUALPD), conducted under a uniform protocol developed and monitored by the MDS (Skorvanek 2017). In this cohort, consecutive patients from 25 tertiary Movement Disorder centers from 15 countries were enrolled. Only PD patients diagnosed according to international recognized criteria (Hughes 1992) and from countries using an officially validated language version of the MDS-UPDRS were eligible for inclusion into the study (Goetz 2014). The study was approved by the Local Ethics Committees in all participating centers. All patients participated voluntarily and gave written informed consent. The investigation was performed according to the Declaration of Helsinki.

**Measures**

*Sociodemographic* data, including age, gender, length of education, as well as information on disease duration and antiparkinsonian medication were collected. The levodopa equivalent daily dosage (LEDD) was calculated according to Tomlinson et al. (2010).

The MDS-UPDRS is a four-subscale combined scale which comprehensively assesses the symptoms of PD. It consists of: Part I - non-motor experiences of daily living (nmEDL) including 13 items – 6 semi-structured interview, 7 self-reported items; Part II - motor experiences of daily living (mEDL) including 13 self-reported items; Part III - motor examination (mEx) including 18 items (33 scores); and Part IV - motor complications (mCompl) including 6 items assessed in a semi-structured interview (Goetz 2008). All items are scored on a scale from 0 (normal) to 4 (severe), total scores are obtained from the sum of the corresponding item scores. English, Estonian, French, German, Hungarian, Russian, Slovak and Spanish language versions of the MDS-UPDRS have been used in this study. The disease stage was assessed by the original Hoehn & Yahr scale (H&Y), which is applied to gauge the course of disease over time (Hoehn 1967).

Health Related Quality of Life (HRQoL) was assessed using either stand-alone or nested version of the 8-item Parkinson’s Disease Quality of Life Questionnaire (PDQ-8) (Peto 1995, Horvath 2017). It is a disease-specific self-administered questionnaire comprised of 8 questions, each of them using a five
points ordinal scoring system (0=Never to 4=Always or cannot do at all), from which a single summary index can be calculated.

**Statistical analyses**

Statistical analyses were performed using the statistical software programs “IBM SPSS Statistics” version 22.0 for Windows (IBM, Armonk, NY), “R” (public domain) and “Stata” (StataCorp, College Station, TX). First, the demographic and clinical characteristics of our study cohort were described. The prevalences of Postural instability gait disorder-dominant (PIGD), Tremor-dominant (TD) and Indeterminate PD subtypes were calculated based on previous report of Stebbins et al. (2013) and mean PDQ8 scores were calculated for each of these groups. Subsequently, hierarchical multiple linear regressions, controlling for selected covariates, were performed to study the relationship between the MDS-UPDRS and PDQ-8. The first regression assessed the relationship between the 4 MDS-UPDRS Part scores and PDQ-8, controlled for age, gender, length of education, LEDD and disease duration. The second regression assessed the relationship between individual items from those Parts demonstrating a significant relationship to the PDQ-8 in the first regression analysis, controlled for age, gender, length of education, disease duration, LEDD and motor status. Finally, a Least Absolute Shrinkage and Selection Operator regression analyses (LASSO analysis), including bootstrap replication, was performed to study the relationship between PDQ-8 and all individual MDS-UPDRS items, controlled for age, gender, years of education, LEDD and disease duration. LASSO regression analysis, used in statistics and machine learning, performs both variable selection and regularization in order to enhance the prediction accuracy and interpretability of the statistical model it produces. Thus, the advantage of this method is the possibility to study a large number of variables in a single model. LASSO analyses were performed independently in statistical softwares “R” and “Stata”.

**Results**
Mean age of the 3206 enrolled patients was 65.76±10.6 years, 1737 were men (54.2%), mean disease duration was 7.6±5.8 years. Majority of the enrolled patients were in H&Y stages II and III (51.6% and 24.1% respectively), 1751 patients (54.6%) had reported motor fluctuations. Majority of language datasets were recruited in a single country with exception of the Russian (Estonia, Russia) and Spanish (Argentina, Chile, Colombia, Cuba, Ecuador, Mexico, Spain, USA) datasets. Mean PDQ8 score was 28.7±19.9 points (95%CI = 3-66). PIGD-dominant PD subtype was identified in 1790 patients (61.4%) with mean PDQ8 score of 34.6±20.4 points; TD subtype in 793 patients (27.2%) with mean PDQ8 score of 21.7±16.5 points; and Indeterminate subtype in 333 patients (11.4%) with mean PDQ8 score of 25.4±16.0 points. Detailed characteristics of the study cohort were described previously (Skorvanek 2017).

**Relationship of MDS-UPDRS parts to HRQoL**

In a multiple regression analysis model with MDS-UPDRS Part scores, 83.3% of the model was explained by MDS-UPDRS Part II (R2/ΔR2 – 71%, Beta – 0.43) and MDS-UPDRS Part I (R2/ΔR2 – 12.2%, Beta – 0.36), respectively. Other MDS-UPDRS parts, as well as other sociodemographic factors, did not contribute significantly to this model. Thus, further regression analyses were aimed at individual MDS-UPDRS part I and II items.

**MDS-UPDRS part I items and PDQ-8**

In a model with MDS-UPDRS Part I items, controlled for sociodemographic variables and MDS-UPDRS Part III score, the most important determinants of worse HRQoL, contributing to the model in total sample and in patients with motor fluctuations, were MDS-UPDRS Part III score, followed by Fatigue, Pain, Depressed mood and Apathy (see table 1). Other MDS-UPDRS Part I items as well as sociodemographic factors did not contribute significantly to the model.

**MDS-UPDRS part II items and PDQ-8**

In a model with MDS-UPDRS Part II items, controlled for sociodemographic variables and MDS-UPDRS Part III score, the most important determinants of worse HRQoL, contributing to the model in
total sample and in patients with motor fluctuations, were Dressing, followed by Doing hobbies, Freezing, Speech and Tremor. MDS-UPDRS Part III score, other MDS-UPDRS Part II items and sociodemographic factors did not contribute significantly to this model (see table 2).

**LASSO analyses of relationship between all individual MDS-UPDRS items and PDQ-8**

In the LASSO analysis, assessing the relationship between all MDS-UPDRS items and PDQ-8, 17 MDS-UPDRS items (6 Part I items, 7 Part II items, 3 Part III items and 1 Part IV item) reached a coefficient of >1. Out of the five items with highest correlation to worse HRQoL, 4 items were non-motor, including Depressed mood, Apathy, Pain and Fatigue (see table 3). The remaining MDS-UPDRS items and other sociodemographic factors did not exceed the coefficient of 1. These results were confirmed with slight differences in both statistical softwares “R” and “Stata”.

**Discussion**

To the best of our knowledge this is the largest study looking at HRQoL in PD population and the first to analyze the relationship between all individual MDS-UPDRS items and HRQoL. In agreement with previous studies (Martinez-Martín 2011, Skorvanek 2015a), highest relationship between HRQoL and MDS-UPDRS was found for Part 2 (mEDL) and Part 1 (nmEDL), respectively, while Part 3 (mEx) and Part 4 (mCompl), as well as all socio-demographic factors and LEDD, did not contribute to the model significantly.

**Physical symptoms**

Importance of restrictions in ADLs resulting from motor impairment for deteriorating the HRQoL, rather than motor status itself, has been well-documented (Kadastik Eerme 2015). The mEDL items which emerged as the most important contributors to HRQoL were Dressing, Chewing and swallowing, Speech, Doing hobbies, Tremor, Freezing and Getting out of bed. The mEDL item with highest relationship to HRQoL in both statistical models was Dressing, which is a major indicator of functional independence. Inability to dress and undress oneself increases the dependence of patients on their carers and clearly decreases their HRQoL. (Rahman 2008) Another important contributor to
HRQoL in our study, problem with performing one’s hobbies, changes significantly patient’s life routines and is often associated with decrease in social activities. Fukunaga et al. (1997) found that the comprehensive HRQoL in PD was lowest in terms of social activities, hobbies and leisure activities, followed by work and subjective HRQoL. Axial symptoms such as falls and postural instability have been repeatedly identified as the major determinants of worse HRQoL in PD patients (Muslimovic 2008). This finding, however, was not replicated in our cohort, as only mEDL item Freezing and mEX item Gait, but not postural instability or falls items, were significant contributors to HRQoL. The mEx item Gait, however, evaluates mostly the ability to walk unaided and higher scores in this item are associated with worse mobility, postural stability and higher risk of falls. Freezing may also significantly increase the risk of falls and decrease functional mobility. Moreover, Moore et al. (2007), have shown, that freezing of gait affects HRQoL in PD patients beyond its relationship with mobility and gait. Speech and swallowing-related HRQoL decreases with progression of PD (van Hooren 2015). These symptoms are often associated and their cumulative prevalence may reach up to 90%. Moreover, dysphagia may be associated with increased risk of malnutrition, increased costs of healthcare and eventually with increased risk of aspiration pneumonia, which might be the most life-threatening dysfunction in PD (Kalf 2012).

Most of the previous studies showed that tremor, compared to other motor manifestations such as axial symptoms had no or lower relationship to HRQoL and similarly patients with PIGD subtype of PD had worse HRQoL compared to TD subtype (Schrag 2000, Wu 2016), what was replicated also in our study. In contrast to these findings, the mEDL item Tremor contributed significantly to both of the statistical models in our cohort and was even a better predictor of HRQoL than the individual items representing axial symptoms. This may be due to the fact, that majority of previous studies have evaluated the tremor scores based on resting tremor items derived from the motor examination, typically in ON state, while the mEDL item of the MDS-UPDRS assesses all types of tremor including action tremor, tremor related to motor fluctuations and OFF states and is related more to the functional disability resulting from tremor, than to raw score of its severity. What influences the
HRQoL is what is perceived by the patients. Part II item Tremor is directly perceived by the patient and concentrates in only one item all perceived aspects related with tremor, including interference with other ADLs, stigma, anxiety caused by its presence, fluctuations in severity, etc. Also, the mEx item Kinetic Tremor of right hand, but none of the resting tremor items was a contributor to the LASSO model. Thus, for future studies, the mEDL item Tremor seems to be more suitable for screening of tremor-related HRQoL than motor examination items evaluating tremor.

**Non-motor symptoms**

In line with previous reports, the overall burden of NMS was more relevant in regards to HRQoL than motor status (Martinez-Martin 2011, Skorvanek 2015a). Four out of five most important contributors to HRQoL in the LASSO analysis were NMS – Depression, Apathy, Pain and Fatigue, while two other NMS items - Hallucinations and Dopamine dysregulation syndrome (DDS) contributed to the model as well.

Similarly, to other studies (Balestrino 2017, Schrag 2006), depression was the most significant individual MDS-UPDRS item contributing to worse HRQoL in our cohort. Depression is a common NMS, with prevalence reported in the range of 7-76% depending on the method of its assessment (van Uem 2016). It has been associated with risk factors such as increasing age, female gender, personal or family history of depression and somatic comorbidities (Leentjens 2002). While depression affects HRQoL directly, it may affect HRQoL also indirectly through increasing the severity or worsening perceptions of other NMS, such as fatigue or apathy, which are typical comorbid symptoms of depression, but may be present also independently in PD (Skorvanek 2015b).

Depression may also influence HRQoL indirectly via worsening of ADLs (Lawrence 2014). Pain may be present in up to 85% of PD patients and has different subtypes including musculoskeletal, neuropathic, dystonic, radicular and other types of pain (Valkovic 2015). It may have detrimental impact on physical functioning and similarly to depression may worsen HRQoL indirectly through its influence on ADLs (Roh 2009, Rana 2012). PD subjects with pain were found to be more depressed and vice versa depression may increase the severity and periodicity of pain (Valkovic
2015). Pathophysiology of pain in PD is rather heterogeneous, what should be taken into consideration especially when treatment decisions have to be made. In this regard, proper pain phenotyping should be performed, as some subtypes, such as dystonic pain, may respond well to dopaminergic medication, while others, such as neuropathic pain, do not (Ford 2010).

Fatigue is one of the most frequent NMS in PD, present in up to 80% of patients (Skorvanek 2015b). In one of the first studies of fatigue in PD, 15–33 % of patients rated it as their most disabling symptom, and more than half rated fatigue among their three worst symptoms (Friedman 1993).

Primary PD-related fatigue (Kluger 2016), has been previously linked to serotonergic dysfunction of the basal ganglia and limbic structures (Pavese 2010). Secondary fatigue in PD may be also a consequence of many other disorders, such as anemia, congestive heart disease, sleep disorders, depression or apathy. Fatigue is often levodopa non-responsive and despite its relevance, the treatment options for primary PD-related fatigue are rather limited and present a major challenge for future research.

Compared to some other NMS, the spectrum of DDS and impulse control disorders (ICDs), encompassing symptoms such as hypersexuality, pathological gambling, pathological shopping, binge eating and other phenomena, has a relatively low prevalence, estimated at around 14% (Evans 2009). ICDs are present especially in younger PD patients and are most commonly linked to dopaminergic medications, especially dopamine agonists, but also L-dopa. They have been previously associated with worse HRQoL, and once present may severely affect patient’s social and family life (Leroi 2011, Kovacs 2016).

Given, that cognitive impairment has been identified as one of the major sources of disability in PD (Leroi 2012), it is surprising, that it did not contribute to HRQoL in any of the models used in our study. The construct of HRQoL is understood as self-assessment based on subjective and self-controlled judgement. Disturbances such as loss of memory and problems of language may challenge the self-assessment and turn its content unreliable (Martinez-Martin 2006). Cognitively impaired
patients, thus, tend to neglect some aspects of HRQoL measured by standard scales and specific instruments should be used in these settings. Moreover, Gallagher et al. (2012) have previously shown, that the MDS-UPDRS item Cognitive impairment did not correlate highly with other measures of cognitive functioning. Nevertheless, other NMS contributing to worse HRQoL, apathy and hallucinations, are both strongly linked to cognitive impairment. They may both herald the onset of dementia and are significantly more prevalent among cognitively impaired PD patients (Dujardin 2009, Giladi 2000) and thus, it is possible, that these items may cover the variance associated with the Cognitive impairment item in our regression analyses models. Similarly, to cognitive impairment, none of the autonomic and sleep items had a significant relationship to HRQoL in our study.

**Fluctuations**

Functional impact of fluctuations was the only mCompl item related to worse HRQoL in our cohort. While historically research focused on motor fluctuations, it is becoming evident that non-motor symptoms such as mood disorders, cognition, fatigue and pain also show fluctuations after chronic levodopa therapy. It is now also generally accepted that non-motor fluctuations (NMF) do not represent non-motor reactions to motor OFF states, but can be conceptually separated from motor fluctuations, despite their frequent temporal co-occurrence (Classen 2017). Functional impact of fluctuations on HRQoL is therefore most likely mediated not solely through motor symptoms, but also through co-occurrence of NMF such as fatigue, depression, pain and others (Rieu 2016), which have been identified as significant contributors to HRQoL in our study.

**Strengths and limitations**

Enrollment of a large international cohort of PD patients representative of different disease stages, subtypes, cultural and language backgrounds addressed power limitations of some of the previous studies. Moreover, the sample size enabled us to perform more sophisticated statistical analyses, such as the LASSO, and evaluate the large number of individual MDS-UPDRS items and other
variables in a single model. On the other hand, the cross-sectional design of the study does not allow us to further explore the causal pathways between the studied variables. Also, the sample comes from specialized settings. Therefore, results may be not immediately applicable to general PD population.

**Conclusions**

MDS-UPDRS seems to be an easy and practical tool for HRQoL-related studies in PD, as it evaluates majority of relevant manifestations of PD and also the impact these symptoms have on their functioning. Results of our large international study show, that ADLs and NMS, rather than motor status per se are the major determinants of HRQoL in PD patients. NMS items related to mood, fatigue and pain seem to be the most important determinants of HRQoL in PD. Future reports on this cohort should determine potential differences among HRQoL determinants in different subsets of PD patients and especially in different language, ethnic and cultural settings, which have not been analyzed in the literature so far.

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