

Concordance between severity of disease, prevalence of nonmotor symptoms, patient-reported quality of life and disability and use of medication in Parkinson's disease

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Abstract The aim of this study was to test the concordance between disease severity, prevalence of nonmotor symptoms, age, health-related quality of life (HRQoL), disability and medication use in patients with Parkinson's disease (PD). Severity was classified with the Hoehn and Yahr (HY) scale and Levodopa Equivalent Daily Dose (LEDD) calculated. HRQoL was evaluated with the SF-36, disability with the WHO-DAS II and nonmotor symptoms with the NMSQuest. Patients were clustered using SF-36 and WHO-DAS II into three groups covering the continuum from low disability and HRQoL, to severe disability and HRQoL decrement. Contingency Coefficient were used to verify the relationships between clusters and HY stage; ANOVA to evaluate differences in NMS, age and LEDD between clusters; odds ratio to test the likelihood of taking levodopa or dopamine agonist and being member of the three clusters; *t* test to evaluate differences in LEDD between patients with $HY \geq 3$ or ≤ 2 . Eighty-six patients were clustered: 48 had low disability and HRQoL decrement, 18 intermediate disability and HRQoL decrement and 20 high disability and HRQoL decrement. A significant relationship was found between PD severity groups, HRQoL and disability profiles. No differences for age and

LEDD were observed in the three groups, and those with more disability and lower HRQoL reported a higher number of nonmotor symptoms; patients in $HY \geq 3$ were prescribed higher doses of drugs. In conclusion, we found a substantial concordance between PD staging, prevalence of nonmotor symptoms and patient-reported HRQoL and disability measures. In our opinion, the SF-36 and the WHO-DAS II can be used for profiling patients.

Keywords Disability · Health-related quality of life · Parkinson's disease · Nonmotor symptoms · Levodopa equivalent daily dose · LEDD

Introduction

Parkinson's disease (PD) is one of the most common progressive neurodegenerative diseases occurring in ageing populations. Its prevalence is estimated at 0.3% in the entire population, increases at about 1% over 60 years of age and, in the highest age groups, it can reach 4%, while incidence is estimated between 8 and 18/100,000 persons-year, with a sharp increase for the group aged over 60 [1]. The cardinal motor symptoms of PD are bradykinesia/akinesia, rest tremor, rigidity and impairment of postural reflexes and other clinical features include hypomimia, dysarthria, dysphagia, micrographia, gait disorder, freezing and dystonia [2]. The presence of nonmotor symptoms is an almost neglected issue, but in recent years their relevance has been increasingly recognised [3, 4]. As a recent review has shown, there are many nonmotor symptoms, broadly categorized into cognitive, affective, sleep, autonomic and sensory [5]. Some of these signs (e.g. olfactory deficit, REM-behaviour disorders, excessive daytime somnolence, depression and anxiety, constipation and

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erectile dysfunction) may precede motor impairment, but they could also represent adverse effects of medications. Treatment approach to PD is complex and requires the integration of different types of medication, including Levodopa, Dopamine Agonists, catechol-*O*-methyl transferase (COMT) inhibitors, type B monoamine oxidase (MAOB) inhibitors as well as other agents, such as antiviral [6]. Levodopa is commonly the initial treatment option and usually determines early improvement in motor symptoms that can be maintained up to 5 years. Dopamine agonists are efficacious as well and, in contrast to levodopa, do not provoke dyskinesias, but may cause gastrointestinal and psychiatric side effects. Treating for autonomic and psychological symptoms, as well as for postural instability, usually requires a complex management of patients which include adjusting prescribed therapies [6], e.g. adding antipsychotics or antidepressants, as well as other interventions such as physical therapy [7].

Both motor and nonmotor symptoms were found, in recent publications, to be independent determinants of reduced health-related quality of life (HRQoL) and increased disability in PD patients. Among motor symptoms, the most common and relevant determinants found are dyskinesias, motor fluctuations, axial impairment, lower extremity strength and freezing of gait [8–12]. Among nonmotor symptoms, depression, dementia, psychosis, cognitive impairment, apathy and sleep disorders (such as urinary incontinence, restlessness, morning fatigue and somnolence) were found to be the most common and relevant determinants of reduced HRQoL and increased disability [8, 9, 11, 13, 14].

Parallel to this, age, age of onset and disease severity, irrespectively of type of impairment, were also found to be among the most relevant predictors of HRQoL and disability [9, 15, 16]. In particular, it has been demonstrated that the onset of balance impairments, and therefore the transition between Hoehn and Yahr (HY) [17] stage 2 and 3 is a pivotal stone in PD-related disability [15]. Social support was also found to be an independent predictor of HRQoL [18].

Health-related quality of life measurement in PD research is almost standardised. In a recent systematic review [16], in which 29 papers were selected, two HRQoL measures, namely the SF-36 and the PDQ-39 [19, 20], were used in 21 of these papers. With regard to the measurement of disability, strategies include the utilisation of both physical performance measures [21] and multidimensional disability assessment scales such as the Unified Parkinson Disease Rating Scale (UPDRS) [22] or the Schwab and England scale [23].

However, none of these scales measure disability according to the framework endorsed by WHO's International Classification of Functioning, Disability and Health

(ICF), in which disability is intended to arise, in an individual, from the interaction between his/her health state and the features of the context in which he/she lives [24]. The inclusion of the context is of primary relevance as the natural progression of PD might determine an increase in utilisation of resources from the context, in particular the support from relatives or other persons, which have profound implications for continued maintenance in the community [25]. As PD severity progresses, disability and HRQoL are expected to worsen as well, but the relationship between disease severity, including both motor and non-motor symptoms, and outcome measures such as disability and HRQoL are not systematically evaluated. This study therefore aimed at evaluating the degree of concordance between disease severity, measured in terms of disease stage and prevalence of nonmotor symptoms, use of pharmacological therapies, patients' age and self-reported HRQoL and disability.

Materials and methods

Study design and procedure

The study design was cross-sectional, and patients were consecutively enrolled at the division of Neurology I—Movement Disorders of the Neurological Institute C. Besta of Milan. Patients were selected if they had a diagnosis of PD, according to UK Parkinson's Disease Brain Bank criteria [26]. Patients selected for technological PD treatment (e.g. surgical approaches such as deep brain stimulation, implantation of infusion pump for duodopa or apomorphine), those with diagnosed psychiatric comorbidities or cognitive impairment, those enrolled in clinical trials in the previous 3 years and those unable to give their consent were excluded. The study was approved by the institute's ethical committee, and all enrolled patients signed an informed consent form.

Progression of PD was defined by HY classification of Parkinson's disease [17], a five-stage classification system: stage 1 and 2 describe patients with one-sided and bilateral symptoms, without balance impairment; stage 3 and 4 describe patients with moderate or severe symptoms and with balance impairment; stage 5 describes patients whose symptom severity requires them to be wheelchair-bound or bedridden unless assisted. Nonmotor symptoms were evaluated with the Non Motor Symptoms Questionnaire (NMSQuest) [27], a 30-item screening of presence of nonmotor symptoms. Nine subscales (Digestive, Urinary, Attention and Memory, Hallucinations/Delusions, Depression/Anxiety, Sexual, Cardiovascular, Sleep, Miscellany) and a general score are available: higher scores reflect higher prevalence of nonmotor symptoms.

Disability was assessed with the WHO-DAS II, a 36-item disability assessment tool that examines the difficulties experienced in the previous month due to the presence of a health condition [28, 29]. Items are rated on a five-point scale, from no problems to complete problems/cannot do the activity. WHO-DAS II is composed of an total score and of six subscores: understanding and communicating; getting around; self care; getting along with people; life activities (divided into household and work); and participation in society. Scores range between 0 and 100, with higher scores reflecting greater disability. Both a 36-item and a 32-item summary score are available: the second is used in case the respondent does not perform work activities.

HRQoL was measured with the 36-item Short-Form Health Survey (SF-36) [30], a generic tool which measures eight general health concepts regarding physical and mental status: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Each scale is scored on a 0–100 scale, with higher scores reflecting better HRQoL. Two main scores are available to summarize these scales: physical composite score (PCS) and mental composite score (MCS), which are norm-based scores (mean 50 and standard deviation 10).

Use of therapies were recorded in terms of utilisation of levodopa, dopamine agonists (e.g. Pramipexole, Ropinirole or Cabergoline), COMT inhibitors (e.g. Entacapone), MAOB inhibitors (e.g. Rasagiline) and other agents such as Amantadine. Levodopa equivalent daily dose (LEDD) was calculated based on available conversion formulae [31].

Statistical analysis

Demographic and clinical information were reported using descriptive statistics as needed. The One-Sample Kolmogorov–Smirnov Z test confirmed that distribution of SF-36 PCS and MCS, WHO-DAS II summary score, LEDD, age and NMSQuest total score corresponded to a normal distribution, thus justifying the utilisation of parametric procedures.

Patients were grouped into three classes on the basis of the summary scores of SF-36 and WHO-DAS II using K-Means Cluster Analysis: *F* statistic was employed to determine the contribution of each variable in separating these groups, and Bonferroni post-hoc test was employed to assess differences between each pair for the three variables. This allowed covering the continuum from mild disability and mild HRQoL decrement to high levels of disability and substantial HRQoL decrement.

To evaluate strength and significance of the relationships between cluster groups and PD staging, cross tables

with Contingency Coefficient statistic were used. To evaluate if nonmotor symptoms prevalence and patients' age were different in the three groups, One-Way ANOVA with Bonferroni post-hoc test was used. With regard to medication regimen, patients were divided on the basis of what kind of medication they were prescribed, defined as use of levodopa and use of dopamine agonist. The odds ratio was calculated to test the association between the treatment regimen and cluster membership. Moreover, differences in amount of LEDD were evaluated using One-Way ANOVA with Bonferroni post-hoc test for comparing subjects among the three clusters and with Student's *t* test between subjects in HY score ≤ 2 and HY score ≥ 3 . *P* value < 0.05 was used to set statistical significance; data have been analysed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

Results

In total, 96 patients (64 males, mean age 64.1, SD 11.3) were enrolled. However, for ten cases, nine of whom were males, the section related to household tasks of the WHO-DAS II was not filled in because these persons did not usually take care of household tasks, resulting in ten missing WHO-DAS II global scores. Therefore, sample used for cluster analysis was composed of 86 patients (55 males, mean age 63.1, SD 11.6): 62 were married or cohabitating, 36 achieved a high education level and 19 were employed. With regard to medication use, 52 patients were taking a therapy based on the association of levodopa and dopamine agonist, 19 patients were taking levodopa alone, 11 were taking dopamine agonists alone and three were taking Amantadine alone. Mean LEDD was 756.2 mg/die (SD 498.5). In total, 71 subjects were taking levodopa (alone or in combination) and 64 subjects were taking dopamine agonist (alone or in combination).

The result of K-Means Cluster Analysis is reported in Table 1. Patients have been divided into three groups on the basis of WHO-DAS II summary score and of SF-36's PCS and MCS. Although each scale is useful to identify cluster membership, as showed by high *F* values, WHO-DAS II summary score is the variable that most contributes in separating clusters ($F = 94.9$). Cluster A was composed of 48 patients (37 males) that reported low disability and low HRQoL decrement; Cluster B was composed of 18 patients (12 males) with intermediate disability and HRQoL decrement; Cluster C was composed of 20 patients (6 males) with high disability and HRQoL decrement. Post hoc test revealed significant differences between Clusters A and B for SF-36 MCS score only, and between Clusters B and C for both SF-36 PCS and WHO-DAS II summary score.

Table 1 K-Means Cluster Analysis: patients divided into three groups according to disability levels and HRQoL decrement

	Clusters			<i>F</i>
	A	B	C	
Dtot	11.7 (9.6–13.8)	15.6 (12.0–19.3)	40.8 (36.1–45.4)	94.9
PCS	43.2 (40.8–45.6)	43.4 (40.5–46.4)	30.7 (28.2–33.2)	23.6
MCS	53.8 (52.4–55.3)	37.6 (34.9–40.3)	38.0 (33.1–42.8)	62.3

For each group, cluster centroids and 95% Confidence Interval are reported

Dtot WHO-DAS II summary score, *PCS* physical composite score, *MCS* mental composite score

Cluster A (48 patients, 37 males), low disability and HRQoL decrement; Cluster B (18 patients, 12 males), intermediate disability and HRQoL decrement; Cluster C (20 patients, 6 males), high disability and HRQoL decrement

The relationship between the three groups obtained with cluster analysis and HY staging of PD classes is reported in Table 2. Majority of patient in Cluster A were in HY stage 1 or 2 (83.3%), majority of those in Cluster B were in HY stage 2 (72.2%) majority of patients in Cluster C were in HY stage 3 or 4 (65%). Contingency Coefficient index was 0.458 and accounted for a significant but moderate relationship between HY staging and severity groups based on disability and HRQoL decrement. With regard to the use of different medical therapy regimens, the calculation of odds ratio showed that patients taking levodopa had a higher probability of being in Cluster C (OR 5.12), and lower of being in Clusters A (OR 0.58) and B (OR 0.61), while those taking dopamine agonists were more likely to be in Clusters A (OR 1.51) and B (OR 1.84) than in Cluster C (OR 0.38).

The results of One-way ANOVA are reported in Table 3. No differences were observed for age and total LEDD, while with regard to nonmotor symptoms, Bonferroni post-hoc test showed that patients with higher disability and higher HRQoL decrement reported a higher number of nonmotor symptoms compared with the other two group of patients. *t* test showed that patients classified in HY classes I and II were prescribed lower medication dosage, in terms of LEDD, than those in HY classes III and IV (HY score ≤ 2 , mean 678 mg/die, 95% CI 559–797 mg/

die; HY score ≥ 3 , mean 946 mg/die, 95% CI 765–1,128 mg/die; $t = 2.46$, $P = 0.016$).

Discussion

In this paper we evaluated the concordance between HRQoL and disability, measured with the WHO-DAS II and the SF-36, PD staging, evaluated with the HY scale, prevalence of nonmotor symptoms, screened with the NMSQuest and utilisation of medication, evaluated through LED and through the pharmacological class. Our results account for a significant, even if not strong, concordance between the clinical aspects of the disease and employed outcome measures, while neither age nor medication dosage was different between the three groups. Parallel to this, patients taking levodopa were five times more likely to be in the most severe cluster, while those taking dopamine agonist were three times less likely to be in the most severe cluster.

Patients in the most problematic group, that present with lower HRQoL and higher disability, are more likely to be in higher HY stages (3 or 4) and have significantly more nonmotor symptoms compared with both patients in the less problematic group and with that in the intermediate one. Patients in the two less problematic groups, on the contrary, report similar prevalence of nonmotor symptoms but are differently located with regard to HY stages. In fact, those with lower disability and HRQoL decrement are more likely to be HY stage of 1 or 2, while patients in the intermediate cluster are more likely to be in stages 2 and 3.

When HY stages are taken into account, it is evident that stages 1, 2 and 4 are, in a sense, “well located” in the three clusters: stage 1 is prevalent in the less problematic cluster, stage 2 in the first two clusters and stage 4 is present only the most problematic cluster. On the contrary, a more balanced distribution is observed for stage 3, which is prevalent in the third cluster and, with a little lower frequency, also in the first one. In sum, while the first and the last clusters seem to be well defined and well in relation

Table 2 Frequency cross tabulation: HY staging and its relationship with disability and HRQoL decrement cluster groups

HY staging	Clusters			Total
	A	B	C	
I	9	1	1	11
II	31	13	6	50
III	8	4	10	22
IV	–	–	3	3
Total	48	18	20	86

Contingency coefficient = 0.458

$P = 0.001$

Table 3 Differences in age, NMSQuest total scores and LEDD in patients included in different clusters

	Clusters			<i>F</i>	<i>P</i> value
	A	B	C		
Age	64.0 (60.7–67.2)	62.4 (55.9–69.0)	65.1 (59.8–70.5)	0.3	0.78
NMSQuest-T	8.0 (6.8–9.2) ^a	9.3 (7.2–11.3) ^b	14.3 (11.7–16.8) ^{a, b}	14.4	<0.001
LEDD	761.5 (606.2–916.8)	624.2 (409.7–838.7)	817.2 (602.6–1,031.9)	0.77	0.47

Values are reported as mean and 95% Confidence Intervals

Age is reported in years and LEDD in mg/die

Bonferroni post-hoc test: ^a difference is significant between patients in Cluster A (low disability and HRQoL decrement) and Cluster C (high disability and HRQoL decrement); ^b difference is significant between patients in Cluster B (intermediate disability and HRQoL decrement) and Cluster C (high disability and HRQoL decrement)

with HY stages, the intermediate cluster is not well defined and not well described on the basis of clinical features of patients. This pattern is observed in approximately 22% of our PD sample. We speculate that this partial lack of concordance could be explained on the basis of the underlying constructs. In fact, we matched a measure of HRQoL, which is a subjective appraisal of health states, with a measure of disability, which describes the interaction between a health condition and the contextual factors in which patients live. The difference between the first and the second Cluster is accounted only by SF-36 MCS score, while no differences in PCS and WHO-DAS II summary score were observed, implying that decrements in mental health determine a first relevant step in the definition of outcome severity in PD. This result is consistent with the increasingly recognised relevance of nonmotor symptoms on quality of life [13, 32, 33].

In this study we detected a precise association between increased disease severity, high levels of disability and reduced HRQoL. Similar results were described a recent paper which evaluated the determinants of HRQoL in PD patients, evidencing that presence of depression or dementia decreased HRQoL by 15–47% [8]. In addition to this, decrease in mental aspects of HRQoL was found to be associated with a reduction of the ability of the subject to take part in social interactions also in other chronic neurological diseases, such as myasthenia gravis and migraine [34, 35]. More in general, studies that employ generic measures of HRQoL and disability like the SF-36 and the WHO-DAS II concluded that the two outcome measures report complementary and not transposable information, which enable researchers to collect information on the person–environment interaction [34–37]. This information may enable to plan interventions, both at a medical or at a psycho-social level, that keep into account both the clinical status of the patient, that is any case the primary outcome measure, and the daily lived experience of patients and their difficulties. As profiles obtained with the SF-36 and the WHO-DAS II, although related, do not overlap with PD

staging, this procedure could be useful as an alternative research strategy to identify beneficiaries of treatment. The results of this study demonstrate that the SF-36 and the WHO-DAS II are adequate tools for creating groups based on different degrees of disability and HRQoL: longitudinal studies need to be carried out to confirm the validity of this strategy.

A previous paper [38] showed that SF-36 and WHO-DAS II were worst among patients with HY scores ≥ 3 . With this paper we complement previously reported data by adding information on drug consumption. Patients in higher HY categories, in fact, were also those taking higher LEDD, which is clearly associated to increased disease severity and to the need of managing more and more complex symptoms, including motor and nonmotor ones. The association between drug consumption and patient-reported outcome measure is, on the contrary, less clear. In fact, we found no differences with regard to total LEDD among the three groups based on outcome measures' composition. This is of course not completely surprising, since medications are not prescribed on the basis of PD clinical course, and not on the basis of its effects on patients' daily lives. However, parallel to this, we observed that it is possible to detect some degree of association between what kind of medication is prescribed to patients and their levels of disability and HRQoL decrement. In fact, levodopa is mostly prescribed to patients with more severe disability and HRQoL decrement, while those with less disability and better HRQoL are more likely to be on dopamine agonist. This information should, however, be carefully interpreted, as the majority of patients enrolled in this sample were prescribed a combination of levodopa and dopamine agonist, that demonstrated to be effective in reducing fluctuations and motor complications compared to utilisation of levodopa only [39–41].

Our results open the discussion on how much should treatment for PD at different stages could be beneficial in terms of disability reduction or prevention. In fact, different treatment may be beneficial for some kind of

symptoms, thus reducing the disability associated with these symptoms, but at the same time, side effects of medications might generate new symptoms, thus potentially determining differences in disability state. This is, for example, the case of dopamine antagonists, that on one side do not provoke dyskinesia, but can determine psychiatric problems such as those connected to impulse control which, in turn, may determine problems with pathological gambling, sexual disinhibition, or compulsive shopping [6]. Our data, study design, sample composition and sample size do not enable us to define any kind of relationship between treatments, symptoms, PD stage and disability status: future studies, with a larger sample and an adequate length of follow-up should be planned to provide a response to such research questions.

Sample composition and study design represent possible limitation to our result. Sample was in fact composed of a relatively limited number of patients attending a specialized centre, mostly in HY stage 1 or 2; therefore, these results should not be generalized to the whole PD patient population. The cross-sectional design which does not enable to define causal relationships also partially hinders the strength of the relationships that were evidenced in the study. Finally, the utilisation of generic instead of disease-specific HRQoL assessment tool could represent a limitation. However, in a recent paper the psychometric properties of the SF-36, compared with PD-specific HRQoL tools, have been evaluated: the SF-36 showed a superior responsiveness to change, while PD-targeted measures tapped into additional HRQoL content not covered by the SF-36 scales [42]. A comment should be also made on the utilisation of LEDD, which is an increasingly used way to compare patients using a single indicator that accounts for differences in both treatments (e.g. levodopa, dopamine agonist, COMT and MAOB inhibitors) and dosage. Numerous different formulae for calculating LEDD have been developed, and we decided to rely on the indication of a recent systematic review [31]: therefore, it cannot be excluded that the utilisation of a different approach might determine the differences in results.

In conclusion, we have shown that there is a substantial concordance between PD staging, prevalence of nonmotor symptoms, patient-reported HRQoL and disability measures. A second result is that the use of medication, with regard to dosage, is more connected to disease severity rather than patient-reported outcome measures results, while the kind of medication is also associated with patients' outcome in terms of disability and HRQoL. Third, we conclude that the SF-36 and the WHO-DAS II can be used for profiling patients: obtained profiles, although related to PD staging, do not completely overlap with them and provide complementary information. This methodology might also be an alternative research strategy when

beneficiaries of treatment need to be identified: longitudinal studies are needed to confirm the utility of this procedure.

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