Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Handicap as a Measure of Perceived-Health Status in Parkinson's Disease

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ABSTRACT: Background: Handicap is a patient-centered measure of health status that encompasses the impact of social and physical environment on daily living, having been assessed in advanced and late-stage Parkinson's Disease (PD).

Objective: To characterize the handicap of a broader sample of patients.

Methods: A cross-sectional study of 405 PD patients during the MDS-UPDRS Portuguese validation study, using the MDS-UPDRS, Unified Dyskinesias Rating Scale, Nonmotor symptoms questionnaire, PDQ-8 and EQ-5D-3L. Handicap was measured using the London Handicap Scale (LHS).

Results: Mean age was 64.42 (±10.3) years, mean disease duration 11.30 (±6.5) years and median HY 2 (IQR, 2–3). Mean LHS was 0.652 (±0.204); "Mobility," "Occupation" and "Physical Independence" were the most affected domains. LHS was significantly worse in patients with longer disease duration, older age and increased disability. In contrast, PDQ-8 did not differentiate age groups. Handicap was significantly correlated with disease duration ($r = -0.35$), nonmotor experiences of daily living (EDL) (MDS-UPDRS-I) ($r = -0.51$), motor EDL (MDS-UPDRS-II) ($r = -0.69$), motor disability (MDS-UPDRS-III) ($r = -0.49$), axial signs of MDS-UPDRS-III ($r = -0.55$), HY ($r = -0.44$), presence of nonmotor symptoms ($r = -0.51$) and PDQ-8 index ($r = -0.64$) (all $P < 0.05$). Motor EDL, MDS-UPDRS-III and PDQ-8 independently predicted Handicap (adjusted $R^2 = 0.582$; $P = 0.007$).

Conclusions: The LHS was easily completed by patients and caregivers. Patients were mild-moderately handicapped, which was strongly determined by motor disability and its impact on EDL, and poor QoL. Despite correlated, handicap and QoL seem to differ in what they measure, and handicap may have an added value to QoL. Handicap seems to be a good measure of perceived-health status in a broad sample of PD.

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Keywords: Parkinson's disease, London handicap scale, health-related quality of life, patient-centred outcome measure.
Members of the MDS-UPDRS Portuguese Validation Study Group are listed in the Appendix.
Received 4 January 2023; revised 31 May 2023; accepted 11 June 2023.
Published online 7 July 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13826

Patient-centered care is increasingly important in chronic diseases to measure their impact on patients' lives for a holistic disease management.[1] The burden of chronic diseases, such as Parkinson's disease (PD), and the diversity of PD manifestations make the physician-centered clinical evaluation an insufficient approach to patients' unmet needs, calling for the necessity to assess impairments and disabilities. Therefore, the World Health Organization (WHO) developed a classification that distinguishes three different but interconnected concepts: impairment, disability and handicap.[2] Handicap is a patient-centered outcome measure defined as "… a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal, depending on age, sex, and social and cultural factors, for that individual."[1] The term *handicap* was replaced by *participation restriction*[2] to remove the negative implications of the term handicap, and to underline its core feature that environmental factors, in addition to direct effects of disease, significantly restrict the individual from participating in everyday life. The operational definition of handicap still holds true, since the seven domains of participation that can be affected by health states correspond overall to the six dimensions of handicap.[2,3] Handicap shares with the concept of quality of life (QoL) the subjective experience and the influence of contextual factors, however it is more focused, closely defined and more understandable to patients and caregivers.[4,5] A good cross-cultural agreement on the construct of handicap allows for its comparison between different diseases and populations.[6,7] In neurological disorders, handicap has been extensively studied in stroke and multiple sclerosis. Handicap has been measured using the London Handicap Scale (LHS),[4] widely used for epidemiological and research purposes[4,7–10] and, more importantly, to assess the response to rehabilitation interventions.[11] The LHS includes six dimensions of handicap,[6] and it was found to accurately measure the concept of participation restriction.[1,3]

PD is a progressive disorder characterized by several motor and nonmotor symptoms that strongly affects patients' QoL.[12] Several perceived-health status (HS) and health-related quality of life (HR-QoL) tools have been used in PD.[12] Handicap, as a measure of perceived-HS, was previously studied in late-stage PD (LS-PD)[13] patients and in advanced PD patients selected to deep brain stimulation (DBS).[14] Patients in these two distinct groups of advanced PD were disadvantaged in different handicap dimensions, indicating that the LHS may discriminate determinants of handicap between different PD severity groups. To our knowledge, there is no data concerning the use of LHS in earlier stages of PD, and we lack data regarding the sensitivity of LHS to differentiate the handicap of PD patients according to their age and disease duration, irrespective of disease severity. Additionally, as many tools are available to measure perceived-HS and HR-QoL in PD, it is important to determine the added value of measuring handicap over other tools, namely HR-QoL.

We aim to characterize the handicap of a broad sample of PD patients and identify its determinants.

Methods

Study Design

A multicenter cross-sectional study in subjects consecutively recruited between 2014 and 2016 in Brazil and Portugal.

Patients

PD patients were evaluated in movement disorders outpatient clinics of 15 tertiary centers from Brazil and Portugal for the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Portuguese validation study. Patients were included if they were native Portuguese speakers diagnosed with PD according to the UK Parkinson's Disease Society Brain Bank Criteria,[13] with no exclusions on age or disease stage. The study was approved by the local ethics committees and written informed consent was obtained.

Assessment

Data on demographics, clinical history and treatment were obtained by interview. Scales were used in Portuguese version and most (84%) of those patients with levodopa-induced motor complications were assessed in ON. The MDS-UPDRS[15] assesses the nonmotor (part I) (range 0–52) and motor (part II) (range 0–52) experiences of daily living (EDL), the severity of motor signs (part III) (range 0–132) and motor complications (part IV) (range 0–24). A postural instability and gait difficulty (PIGD) sub-score of MDS-UPDRS part III was obtained using axial signs (speech, axial rigidity, arising from chair, gait, freezing of gait, postural stability and posture). The Hoehn and Yahr (HY)[16] scale (range 1–5) stages the severity of PD. The Unified Dyskinesias Rating Scale (UDysRS)[17] evaluates dyskinesias, subjective and objectively (range 0–104). The nonmotor symptoms questionnaire (NMS-Quest)[18] is a 30-item screening questionnaire that assesses the presence of nonmotor symptoms (range 0–30).

HR-QoL was measured using the 8-item Parkinson's Disease Questionnaire (PDQ-8)[19] and the EQ-5D-3 L.[20] The PDQ-8 assesses eight dimensions (mobility, activity of daily living, emotional well-being, stigma, social support, cognition, communication, body discomfort) and a total summary score is obtained by summing the eight items (range 0–100; higher scores reflect worse QoL). The EQ-5D-3L is composed by a descriptive system and a visual analog scale (EQ-VAS). The descriptive system comprises five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each scored with three levels of problems; the digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state and can be converted into a single profile [(EQ-Index; ranges from 0 (death) to 1 (perfect health))]. The EQ-VAS scores between 0 and 100, 100 indicating the best HS. The Clinical Global Impression-Severity (CGI-S)[21] was used to rate clinicians' judgment on the severity of a patient illness (range 1–7; "Normal,

TABLE 1 *Demographics, clinical features and medication use in PD patients*

Characteristic	PD patients (n = 405)
Female, n (%)	157 (38.8)
Age (years), mean (SD)	64.43 (10.309)
Education (years), mean (SD)	8.03 (4.788)
Duration of disease (years), mean (SD)	11.30 (6.545)
MDS-UPDRS-I[b], *median* [IQR, 25th–75th percentile]	12 [8–18]
MDS-UPDRS-II[b], *median* [IQR, 25th–75th percentile]	16 [10–23]
MDS-UPDRS-III[a,b], *median* [IQR, 25th–75th percentile]	39 [29–51]
PIGD[b] score	7 [4–11]
MDS-UPDRS-IV[b], *median* [IQR, 25th–75th percentile]	6.5 [1–10]
Functional impact of dyskinesias	1 [0–3.25]
Functional impact of fluctuations	4 [0–6]
Painful OFF-state dystonia	0 [0–1]
MDS-UPDRS total score[b], *median* [IQR, 25th-75th percentile]	76 [57–99]
HY[a,b] **stage**, *median* [IQR, 25th-75th percentile]	2 [2–3]
UDysRS total score[b], *median* [IQR, 25th-75th percentile]	18 [0–37]
Historical (subjective) sub-score	12 [0–22]
Objective sub-score	0.5 [0–17]
NMS-Quest, *median* [IQR, 25th-75th percentile]	11 [7–15]
Measures of quality of life	
PDQ-8 summary index[c], *median* [IQR, 25th–75th percentile]	31.25 [18.75–43.75]
EQ-5D-3L[d] index, *median* [IQR, 25th–75th percentile]	0.647 [0.514–0.799]
EQ-VAS[d], *median* [IQR, 25th–75th percentile]	65 [50–80]
CGI-S[b], *median* [IQR, 25th–75th percentile]	4 [3–5]
Medication	
Levodopa, n (%)	367 (90.8)
Monotherapy, n	78
In combination, n	289
Agonists, n (%)	256 (63.4)
Amantadine, n (%)	113 (28.0)
COMT inhibitors, n (%)	78 (19.3)
MAO inhibitors, n (%)	107 (26.5)
Anticholinergics, n (%)	24 (5.9)
Apomorphine, n (%)	1 (0.2)
Brain surgery for PD, n (%)	64 (15.8)
Neuroleptics, n (%)	4 (1)
Clonazepam, n (%)	15 (3.7)
Antidementials, n (%)	11 (2.7)
Antidepressants, n (%)	3 (0.7)
Other medications, n (%)	3 (0.7)

Abbreviations: PD, Parkinson's Disease; PIGD, postural instability and gait difficulty sub-score; NMS-Quest, nonmotor symptoms questionnaire; PDQ-8, 8-item Parkinson's Disease questionnaire; EQ-VAS, EQ-5D-3L visual analogue scale; CGI-S, clinical global impression-severity; IQR, interquartile range.
[a]65 (16%) patients were in OFF state at the time of evaluation.
[b]Higher scores indicate a greater severity of impairment.
[c]Higher numbers indicate worse quality of life measurement.
[d]Higher numbers indicate better perceived-health status.

not at all ill" to "Among the most extremely ill patients," respectively).

The LHS[6] evaluates participation and it is a self-completed questionnaire composed by six questions, one for each dimension of handicap (mobility, physical independence, occupation, social integration, orientation and economic self-sufficiency). Each question has six answer options hierarchically describing the degree of handicap for that dimension. The LHS total score is the sum of each dimension's score to which a constant value 0.456 is added. The final score ranges from 0 (maximal handicap) to 1 (no handicap). Caregivers were allowed to fill in the questionnaires in case patients were unable to complete them for themselves.

Statistical Analysis

Descriptive statistics of demographic, clinical and therapeutic data are provided. Categorical variables are reported in count and percentage and continuous variables in means and standard deviations (SD) or medians and interquartile ranges (IQR) according to their distribution. A descriptive analysis of the LHS total score and sub-scores was performed. Nonparametric Kruskal-Wallis test was used to compare continuous variables, and Chi-square test for categorical variables. Nonparametric Spearman's rank correlation coefficients were calculated to analyze the association between variables (coefficients between 0.40 and 0.59 were considered "moderate"). We explored whether the scores of LHS, PDQ-8, EQ-5D-3L and CGI-S differed with disease duration (<5 years; 6–10 years; 11–15 years; > 15 years), age (< 65 and ≥ 65 years-old) and disease severity (HY 1 and 2; HY 3; HY

4 and 5). We further evaluated which PDQ-8 domains were most affected in our sample and which were able to differentiate between groups of disease duration, patient's age and disease severity. Finally, we compared the ability of the LHS and PDQ-8 domains to differentiate these same groups.

Univariable analysis was performed, and variables with moderate to strong association with the LHS score were entered in a multiple linear regression analysis using the LHS total score as dependent variable. No collinearity was observed in multicollinearity tests. Both stepwise and backward analysis were performed with equivalent results. Analyses were performed using SPSS version 24. Two-tailed *P*-value <0.05 was considered statistically significant. A Bonferroni correction was used for multiple comparisons. Coefficients and 95% confidence intervals (CIs) are reported.

Results

Demography, Clinical Features, and Treatment

Demographic and clinical data is described in Tables 1 and 2. A total of 405 PD patients (female 38.8%; Brazil 30.9%, Portugal 69.1%;) were included. Mean age was 64.4 years (SD ± 10.3), mean disease duration 11.3 years (SD ± 6.5) and median HY stage was 2 (IQR [2,3]). Patients from Portugal were older (mean age = 66.3 vs. 60.2, $P = 0.000$), had later disease onset (mean age at disease onset = 55.1 vs. 47.7, $P = 0.000$), had fewer anti-parkinsonian medications (median = 2 vs. 3, $P = 0.003$) and were more frequently submitted to DBS (21% vs. 4%, $P = 0.000$). However, there were no differences on disease severity (HY, MDS-UPDRS, NMS-Quest) and QoL (LHS, PDQ-8, EQ-5D-3L) measures between Brazil and Portugal samples. Motor fluctuations occurred in 70.7% of the patients and 58% had dyskinesias. Fluctuations had a severe functional impact in patients, while the impact of dyskinesias was slight, as measured by items 4.4 and 4.2 of the MDS-UPDRS part IV, respectively. Motor disability was moderate but axial signs were not a major feature. According to the NMS-Quest, memory problems were reported in 51.3% of patients and 49% had concentration difficulties, while apathy affected 39.7% and hallucinations 17.3%. Depressive symptoms were present in 63.4%, insomnia in 44.1% and anxiety in 53.4% of the cases. One third had bulbar symptoms, falls and pain; 59.8% reported constipation, 57.7% urinary urgency and 42.3% symptoms of orthostatic hypotension. Levodopa was prescribed for 90.8% of patients, being 78.7% with adjunct drugs; dopamine agonists were the second most frequent anti-parkinsonian drug. DBS was performed in 15.8% of the patients, none had levodopa/carbidopa intestinal gel and one patient was taking apomorphine. Other associated drugs for dementia and depression were prescribed in 2.7% and 0.7%, respectively.

TABLE 2 *Nonmotor symptoms frequency in PD patients*

NMS-Quest	Patients answering "yes"
1. Drooling, n (%)	119 (30.7)
2. Loss of taste/smell, n (%)	154 (39.7)
3. Swallowing/Choking difficulties, n (%)	139 (35.8)
4. Nausea/Vomiting, n (%)	87 (22.4)
5. Constipation, n (%)	232 (59.8)
6. Fecal incontinence, n (%)	26 (6.7)
7. Constipation (2), n (%)	174 (44.8)
8. Urine urgency, n (%)	224 (57.7)
9. Nocturia, n (%)	219 (56.4)
10. Pain, n (%)	136 (35.1)
11. Weight loss/gain, n (%)	64 (16.5)
12. Memory problems, n (%)	199 (51.3)
13. Apathy, n (%)	154 (39.7)
14. Hallucinations, n (%)	67 (17.3)
15. Concentration problems, n (%)	190 (49.0)
16. Depressive symptoms, n (%)	246 (63.4)
17. Anxiety, n (%)	207 (53.4)
18. Sexual dysfunction, n (%)	211 (54.4)
19. Sexual dysfunction (2), n (%)	161 (41.5)
20. Orthostatic hypotension, n (%)	164 (42.3)
21. Falls, n (%)	123 (31.7)
22. Excessive daytime sleepiness, n (%)	61 (15.7)
23. Insomnia, n (%)	171 (44.1)
24. Intense dreaming, n (%)	187 (48.2)
25. REM sleep behavior disorder, n (%)	209 (53.9)
26. Restless legs, n (%)	188 (48.5)
27. Leg swelling, n (%)	94 (24.2)
28. Hyperhidrosis, n (%)	156 (40.2)
29. Diplopia, n (%)	62 (16.0)
30. Delusions, n (%)	37 (9.5)
Total score, *median* [IQR, 25th-75th percentile]	11 [7–15]

Abbreviations: IQR, interquartile range.

Handicap

LHS values (n = 380) followed a Gaussian distribution. Median total score was 0.653 (IQR [0.493–0.822]) and mean 0.652

TABLE 3 *Total and sub-scores of London Handicap Scale and correlations with total score (n = 380)*

	Mean (SD)	Median (min; max)	Minimum/maximum possible values for total score[a] and sub-score[b]	Pearson correlation with total score	*P*-value
Mobility	0.028 (0.043)	0.038 (−0.108; 0.071)	−0.072/0.071	0.786	0.000
Physical independence	0.029 (0.065)	0.011 (−0.061; 0.102)	−0.061/0.102	0.805	0.000
Occupation	0.006 (0.047)	−0.004 (−0.060; 0.099)	−0.060/0.099	0.736	0.000
Social integration	0.032 (0.031)	0.035 (−0.029; 0.063)	−0.041/0.063	0.713	0.000
Orientation	0.057 (0.063)	0.109 (−0.063; 0.109)	−0.075/0.109	0.670	0.000
Economic self-sufficiency	0.044 (0.044)	0.033 (−0.111; 0.100)	−0.111/0.100	0.433	0.000
Total score	0.652 (0.204)	0.653 (0.112; 1.00)	0/1	1	NA

[a]In the London Handicap Scale total score, 0 indicates maximum of handicap and 1 its absence.
[b]In the London Handicap Scale subscores of the six domains, the minimum value indicates "most severe disadvantage" and the maximum value indicates "no disadvantage."

(SD ± 0.204) (Table 3). No ceiling or floor effects were noted. There was a wide distribution among categories representing different severities of disadvantage on each dimension, therefore LHS seemed to be discriminating well between subjects. The most common categories within each dimension were "no disadvantage" and "minimal disadvantage." Few patients scored "most severe disadvantage" in any of the dimensions. The ones for which more patients recorded a greater disadvantage ("moderate disadvantage," "severe disadvantage" and "most severe disadvantage") were "occupation" (n = 93) and "physical independence" (n = 85). All dimensions correlated with total score. "Physical independence" ($r = 0.805$; $P = 0.000$), "mobility" ($r = 0.786$; $P = 0.000$) and "occupation" ($r = 0.736$; $P = 0.000$) were the dimensions with the strongest correlation with LHS total score, thus the most affected ones (Table 3).

We explored whether handicap differed with disease duration, age and disease severity (Table 4). The sample was divided into *four groups of disease duration*: < 5 years (group 1, n = 69), 6–10 years (group 2, n = 141), 11–15 years (group 3, n = 110) and > 15 years (group 4, n = 85). LHS total score and each dimension sub-score were lower (worse) with longer disease duration (Table 4), which was confirmed by post hoc pairwise comparisons. However, "orientation" and "economic self-sufficiency" domains were significantly different only between group

TABLE 4 *Differences between age, disease severity and disease duration groups of the total and sub-scores of London Handicap Scale (LHS)*

	Mobility	Physical independence	Occupation	Social integration	Orientation	Economic self-sufficiency	LHS total score[a]
Age groups							
<65 yr (n = 175)	0.039 (0.035)*	0.044 (0.062)*	0.014 (0.049)*	0.036 (0.029)*	0.071 (0.058)*	0.042 (0.045)	0.702 (0.187)*
≥65 yr (n = 203)	0.018 (0.047)*	0.017 (0.065)*	−0.000 (0.044)*	0.028 (0.032)*	0.045 (0.065)*	0.046 (0.043)	0.608 (0.209)*
Disease duration groups							
<5 yr (n = 69)	0.047 (0.032)*	0.056 (0.058)*	0.033 (0.055)*	0.045 (0.027)*	0.073 (0.057)*	0.057 (0.043)*	0.767 (0.187)*
6–10 yr (n = 141)	0.029 (0.044)*	0.039 (0.065)*	0.012 (0.051)*	0.034 (0.030)*	0.063 (0.062)*	0.044 (0.046)*	0.678 (0.209)*
11–15 yr (n = 110)	0.025 (0.043)*	0.016 (0.062)*	−0.004 (0.036)*	0.027 (0.030)*	0.052 (0.065)*	0.041 (0.044)*	0.613 (0.186)*
>15 yr (n = 85)	0.013 (0.043)*	0.008 (0.064)*	−0.012 (0.030)*	0.020 (0.032)*	0.042 (0.064)*	0.036 (0.041)*	0.563 (0.177)*
Disease severity groups							
HY I-II (n = 286)	0.040 (0.033)*	0.045 (0.061)*	0.016 (0.049)*	0.037 (0.029)*	0.064 (0.061)*	0.048 (0.042)	0.705 (0.186)*
HY III (n = 83)	0.015 (0.037)*	0.005 (0.061)*	−0.011 (0.028)*	0.029 (0.031)*	0.052 (0.062)*	0.035 (0.043)	0.581 (0.164)*
HY IV-V (n = 34)	−0.048 (0.047)*	−0.042 (0.034)*	−0.033 (0.031)*	−0.004 (0.024)*	0.011 (0.067)*	0.033 (0.059)	0.371 (0.161)*

Note: Values are reported in mean (standard deviation).
[a]In the London Handicap Scale total score, 0 indicates maximum of handicap and 1 its absence; the minimum value of each domain indicates "most severe disadvantage" and the maximum value indicates "no disadvantage."
*$P < 0.05$.

TABLE 5 *Multiple linear regression model. Dependent variable: London Handicap Scale*

Independent variables	B coefficients	95% CI	*P*	Dependent variable	R^2	R^2 Adjusted	*P*
MDS-UPDRS-II	−0.433	−0.012; −0.007	0.000	Total score of London Handicap Scale	0.586	0.582	0.003
PDQ-8 index	−0.311	−0.004; −0.002	0.000				
MDS-UPDRS-III	−0.128	−0.002; 0.000	0.003				

Abbreviations: PDQ-8, 8-item Parkinson's Disease questionnaire; CI, confidence intervals.

1 and 4 after Bonferroni correction ($P < 0.008$). Scores in clinical scales showed similar results (the longer the disease duration, the worse the score), except for MDS-UPDRS-I and NMS-Quest ($P > 0.008$). Scores in PDQ-8, EQ-5D-3L and CGI-S were worse with longer disease duration ($P = 0.000$), however, when adjusting for multiple comparisons, EQ-5D-3L was significantly different only when comparing group 1 with those with longer disease duration (groups 3 and 4) ($P < 0.008$).

Regarding differences in *age*, we found that patients aged 65 or over (n = 216) were more handicapped [LHS total score 0.608 (0.209) vs. 0.702 (0.187), $P = 0.000$] than patients under 65 years (n = 187), having significantly lower scores in all handicap dimensions, except "economic self-sufficiency" ($P = 0.419$) (Table 4). Consistently, older patients had significantly higher scores in motor and nonmotor symptoms of EDL (MDS-UPDRS-I, MDS-UPDRS-II and NMS-Quest), motor severity (MDS-UPDRS-III), disease severity (HY stage and MDS-UPDRS total score) and PIGD score, as well as lower scores in EQ-5D-3L and EQ-VAS (all $P < 0.05$). Interestingly, PDQ-8 was not significantly different between age groups ($P = 0.073$).

Finally, we divided the sample by *disease severity* in HY 1 and 2 (n = 286), HY 3 (n = 83), and HY 4 and 5 (n = 34). LHS total score was significantly different between groups of disease severity [0.705 (0.186) vs. 0.581 (0.164) vs. 0.371 (0.161), $P = 0.000$] (Table 4). Post hoc pairwise comparisons showed the sub-scores of "mobility," "physical independence" and "occupation" worsened significantly with disease severity ($P < 0.017$), while those of "social integration" and "orientation" only differed significantly between the more disabled groups (HY 4 and 5) from the others ($P < 0.017$). Similarly, later disease stages were significantly associated with higher scores in MDS-UPDRS total score, MDS-UPDRS-I, MDS-UPDRS-II, MDS-UPDRS-III, PIGD score and CGI (all $P < 0.017$). Measures of HR-QoL (EQ-5D-3L, EQVAS and PDQ-8) showed significantly worse scores with disease severity (all $P < 0.017$).

In order to explore the distinctive features of the LHS in relation to PDQ-8, we searched for the most affected domains of the PDQ-8 in our sample, and then evaluated which of them were able to differentiate between different age, duration of PD and severity groups. The most affected domains of PDQ-8 were "mobility," "activities of daily living" and "emotional well-being". The total PDQ-8 score did not differ between age groups and only "emotional well-being" showed statistically significant differences between age groups. PDQ-8 significantly worsened with disease duration and severity. On the contrary, LHS and its domains (except "economic self-sufficiency") were significantly different between age, disease severity and duration groups. Thus, LHS and its domains were more sensitive to distinguish age groups than PDQ-8, even when comparing the 3 most affected PDQ-8 domains.

In univariate analysis, the LHS total score had a moderate to strong correlation with the following variables: disease duration ($r = -0.351$), nonmotor (MDS-UPDRS-I) ($r = -0.513$) and motor EDL (MDS-UPDRS-II) ($r = -0.690$), motor impairment (MDS-UPDRS-III) ($r = -0.491$), PIGD sub-score ($r = -0.551$), MDS-UPDRS total score ($r = -0.660$), HY stage ($r = -0.445$), NMS-Quest ($r = -0.514$), PDQ-8 ($r = -0.639$), EQ-5D-3L ($r = 0.557$), EQ-VAS ($r = 0.501$), and CGI-S ($r = -0.545$) (all $P = 0.000$). In multivariate analysis, the variables that best predicted the LHS total score were motor EDL (MDS-UPDRS-II) ($r = -0.690$; $P = 0.000$), PDQ-8 ($r = -0.639$; $P = 0.000$) and motor impairment (MDS-UPDRS-III) ($r = -0.491$; $P = 0.000$) (Table 5). This model explained 58.2% of the variance of LHS total score ($P = 0.003$).

Discussion

Handicap was assessed in a large sample of PD patients ranging from early to later stages of disease. LHS was easy to use with a high rate of completion (94%) and its score followed a Gaussian distribution. This cohort was mild to moderately handicapped. The most common reported categories were "no disadvantage" and "minimal disadvantage." The most affected dimensions were "physical independence," "mobility" and "occupation." Handicap was strongly associated with motor EDL, motor impairment and HR-QoL (PDQ-8). These independent variables explained 58% of LHS total score variance. LHS was able to discriminate handicap regarding different disease duration, age and severity of PD. In contrast, PDQ-8 did not vary significantly between different age groups.

Handicap in PD has been previously studied using the same instrument in late-stage PD (LS-PD) patients[13] and in advanced PD patients selected to DBS.[14] In LS-PD patients, whose clinical picture is dominated by levodopa-resistant motor and nonmotor symptoms,[22] handicap was strongly determined by the presence of dementia and the severity of mental problems and parkinsonism in "off medication".[13] The sample of LS-PD was highly handicapped (mean LHS total score = 0.338), and the most affected dimension was "orientation".[13] In contrast, patients selected to DBS had a moderate handicap (mean LHS total

score = 0.56), whose most affected dimensions were "physical independence" and "social integration," probably related to levodopa-induced motor complications and their impact on social interactions.[14] In fact, the handicap determinants were motor EDL, independence in activities of daily living and severity of peak-dose dyskinesias.[14] Keeping our previous results in mind, we aimed to characterize the handicap of a wider sample of PD patients. Although patients in all HY stages were included in the present study, most had mild to moderate motor and nonmotor symptoms, which may explain the mild to moderate handicap. In particular, dyskinesias and axial motor signs were slight, and NMS were mild,[23] with very few patients taking drugs to treat dementia. Accordingly, general and PD specific measures of HR-QoL showed a good QoL, and physicians rated this sample as "moderately ill." This sample was recruited for the Portuguese validation of the MDS-UPDRS, which may partially explain the above findings. As expected, our cohort had a higher mean LHS total score (less handicap) than reported in later disease stages.[13,14,22] Furthermore, the disadvantage was greater in the dimensions of "physical independence," "occupation" and "mobility", which is consistent with disability being more determined by motor than nonmotor manifestations, specifically in the individual's ability to live an independent life, to occupy her/his time appropriately in the working day and to move without restriction, respectively.[1] It was previously shown that these motor manifestations significantly impact HR-QoL.[24] Conversely, "orientation" and "social integration" were the least affected domains, probably due to the lack of significant cognitive impairment, dyskinesias and axial signs.

The LHS total score correlated with disease duration, motor and nonmotor EDL, and motor and disease severity, showing that handicap increases with disease progression and with the severity of motor and nonmotor symptoms. There was only a weak correlation with motor complications measured by either the MDS-UPDRS-IV or the UDysRS, despite a severe score of the functional impact of motor fluctuations. Handicap was determined by motor EDL, motor impairment and worse QoL by approximately 60%, emphasizing the relevance of motor disability to our patients' handicap.

Our results, together with two previous studies,[13,14] provide relevant data to the study of handicap in PD using the LHS. Firstly, we were able to show that handicap increases with age, disease duration and severity, which upholds with results showing a worse handicap of LS-PD compared to patients selected for DBS and our current less disabled cohort. Secondly, the LHS proved to discriminate between different disease stages of PD, namely detecting the involvement of different dimensions and determinants of handicap in samples with varied disability. Lastly, allowing the characterization of the most affected dimensions, it may be possible to conduct and adapt pharmacological and nonpharmacological therapies programs accordingly. Actually, when Harwood et al[4] developed the LHS, they recognized that handicap reduction was the most important aim of interventions at any level.

The LHS was previously used in other settings[7–9,11] and had its face and construct validity, test–retest reliability[8] and good transcultural agreement[7] proven. The scale was constructed based on the definition of handicap by the WHO International Classification of Impairments, Disabilities and Handicaps[1] concerning the consequences of chronic disease. The handicap concept implies not only the direct impact of chronic disease on an individual's life, but also concentrates the particular circumstances of a given patient (eg, environment, social life, resources and health accessibility)[6] that lead to the handicap process, thus giving a relevant description of the needs and effectiveness of interventions, being an excellent outcome measure. In our sample, LHS was easily completed, its total score had a normal distribution and there was no floor or ceiling effects. There was a wide range of responses of different disadvantages on each dimension, indicating that the scale differentiated well between individuals.

As a measure of perceived-HS, handicap is closely related to the concept HR-QoL.[11,22] Indeed, we found a significant correlation with the HR-QoL measures, namely PDQ-8 and EQ-5D. The strongest correlation was with PDQ-8, which is PD specific and it was also a major independent determinant of handicap in the regression model. Nonetheless, the moderate correlation of LHS with both PDQ-8 and EQ-5D indicate these scales are measuring different components of perceived-HS. Indeed, PDQ-8 was not able to distinguish perceived-HS in different age groups, contrary to LHS. The most affected domains of PDQ-8 were "Mobility," "Activities of daily living" and "Emotional well-being," whilst in LHS were "Physical independence," "Mobility" and "Occupation," suggesting slight differences in the way they capture the impact of PD in different dimensions of a patient's life. Thus, LHS and PDQ-8, although correlated, seem to measure different outcomes and have different sensitivities to capture health status in different age groups of PD patients.

Moreover, while PDQ-8 is a patient-reported scale that provides information about the consequences of PD on physical, mental, and social domains,[24] LHS keeps the subjective perspective of HR-QoL but adds the role of the environment in health status. Handicap emphasizes the role of environmental factors in restricting the individuals from participation in everyday life. In this way, the LHS better identifies problems that can be improved through rehabilitation or occupational therapy, which is an added value compared to PDQ-8 in daily clinical practice. Furthermore, LHS is also recommended for use at the population level, is easy for respondents to complete and sensitive to change,[11] which is an important feature in rehabilitation therapies.

Our study has some limitations. The sample was recruited for the Portuguese MDS-UPDRS validation study, which introduces some bias, namely a low frequency of a significant cognitive impairment and axial motor involvement. Additionally, a formal cognitive and psychiatry assessment was not performed, yet we have indirect data from MDS-UPDRS-I and NMS-Quest. Indeed, the use of the NMS scale instead of the NMS-Quest could have informed us better regarding the severity of NMS, but the scale was not available when the project was started. Thus, the determinants of handicap in our sample may underestimate the role of cognition and other NMS and of axial symptoms for the handicap of PD patients overall. Nevertheless, our sample seems to be representative of the general PD population. Our large, multicenter, consecutively recruited sample and the

use of widely accepted and validated measures is a major strength of the study.

Conclusion

LHS was easily completed by patients and caregivers and provided an overall measure of patients' HS. The scale behaved well in this large sample, it gave insights into the dimensions affected and it proved to be sensitive to identify determinants of handicap according to disease severity. Our results show that handicap seems a valuable outcome of perceived-HS in a broad sample of PD patients, and the LHS seems to add value to the perceived-HS captured by PDQ-8.

Together with our previous studies, we have now measured handicap using the LHS across all stages of PD. Future studies should be performed to assess whether the LHS is sensitive to change after therapeutic interventions.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

D.P.S.: 1A, 2A, 2B, 3A
M.C.: 1A, 1B, 1C, 2A, 2C, 3B
T.S.: 1C, 3B
T.C.V.: 1C, 3B
L.C.G.: 1C, 3B
R.M.: 1C, 3B
A.P.A.: 1C, 3B
S.T.C.: 1C, 3B
A.V.: 1C, 3B
C.G.: 1C, 3B
D.P.M.: 1C, 3B
P.P.L.: 1C, 3B
R.D.M.: 1C, 3B
T.T.: 1C, 3B
C.R.R.: 1C, 3B
A.G.V.: 1C, 3B
V.T.: 1C, 3B
E.R.B.: 1C, 3B
H.A.G.T.: 1C, 3B
H.B.F.: 1C, 3B
M.J.R.: 1C, 3B
A.C.: 1C, 3B
T.L.: 1C, 3B
R.S.: 1C, 3B
N.V.C.: 1C, 3B
M.M.C.: 1C, 3B
A.M.R.: 1C, 3B
V.C.: 1C, 3B
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Disclosures

Ethical Compliance Statement: The authors confirm that the approval of the study was obtained by the Ethics Committee of the Centro Hospitalar Universitário Lisboa Norte on 25 September, 2013, and a written informed consent was obtained by patients. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: No funding was received for this work. The authors have no conflicts of interest related to this work.

Financial Disclosures for the Previous 12 Months: DPS was granted with "Prémio João Lobo Antunes 2021" by Santa Casa da Misericórdia de Lisboa for unrelated research to the work being presented in this article. DPS received honoraria from BIAL. MC received honoraria from Boston and Abbvie. LCG received honoraria from Abbvie, BIAL and Zambon. AV received honoraria from Abbvie and Zambon. CG was granted with "BPI Lá Caixa Seniores 2021" by BPI Fundação Lá Caixa and from Fundação para a Ciência e Tecnologia (FCT–EXPL/SAU-SER/0761/2021CT) for unrelated research to the work being presented in this article. DPM received honoraria from Zambon, Teva and FQM. HAGT received honoraria from Jansen, Teva, and Zambon. HBF received honoraria from Teva, Zambon, Abbvie. MJR received honoraria from Boston and Zambon. APA, RS, and NVC received honoraria from BIAL. AMR received honoraria from Zambon, BIAL and Abbvie. JJF received grants, consultancy and speaker fees and participated in advisory boards for Medtronic, Angelini, Lundbeck, BIAL, Biogen, Abbvie, Sunovion Pharmaceuticals, Zambon, Roche, ONO and SK Chemicals. TS, TCV, RM, STC, PPL, RDM, TT, CRR, AGV, VT, ERB, AC, TL, MMC, VC, FC have no disclosures to report.■

Appendix

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