Research Article

Staging Parkinson’s Disease Combining Motor and Nonmotor Symptoms Correlates with Disability and Quality of Life

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1. Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disorder causing motor and nonmotor symptoms (NMS) that result in disability, loss of patient autonomy, and caregiver burden [1]. In a degenerative disease, it is important to establish clinical stages that allow the determination of disease progression for a patient based on different specific symptoms. Ideally, this clinical graduation should be simple to carry out so that it can be used universally in clinical practice. In the case of PD, and based on the classic motor symptoms of the disease, the Hoehn and Yahr (H&Y) scale is used to describe the progression of PD [2]. The scale was originally described in 1967 and included stages 1 through 5. It has since been modified with the addition of stages 1.5 and 2.5 to help describe the intermediate course of the disease [3]. This rating system has been largely supplemented by, firstly, the Unified Parkinson’s Disease Rating Scale (UPDRS) [4], and more recently, the MDS-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [5], which assess limitation of Activities of Daily Living (ADL) and NMS. However, evaluating the patient using the UPDRS and/or MDS-UPDRS takes time; specialization is required and, importantly, do not allow the patient to be classified into a clearly differentiated stage, and several NMS are not included. Validated tools for assessing NMS such as the NMSQuest [6] and the nonmotor symptoms scale (NMSS) [7] are used both in trials and in clinical practice. Furthermore, it has been demonstrated that NMS are an important determinant and deteriorating factor of the quality of life (QoL) of PD patients [8, 9]. Not only motor symptoms but also NMS increase in their severity and burden over time, increasing patients’ disability, with additional worsening of their QoL, as well as caregivers’ burden and consequential consumption of social resources by increasing societal costs. That is why for staging PD it would be necessary to combine a motor with a nonmotor scale, which would allow the patient to be classified into stages considering both the degree of motor and nonmotor involvement.

Recently, it has been suggested that gradation of PD according to the motor impairment and burden of NMS is an unmet need for an appropriate management of patients [10]. Ray Chaudhuri et al. proposed a PD classification by H&Y staging and NMS burden level and demonstrated a correlation of both H&Y staging and NMS burden to disability and QoL [11]. However, QoL and autonomy for ADL regarding the stage considering both together, motor and nonmotor stages, were not analyzed. The H&Y scale provides quick information about the patient’s condition, but since it does not include NMS, it is not very sensitive to reflect the real impact of that condition. Our hypothesis is...
2. Materials and Methods

PD patients recruited from 35 centers of Spain from the COPPADIS cohort [13] from January 2016 to November 2017 were included in the study. Methodology about COPPADIS-2015 study can be consulted in https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-016-0548-9.

This is a multicenter, observational, longitudinal-prospective, 5-year follow-up study designed to analyze disease progression in a Spanish population of PD patients. The data for the present study (cross-sectional study) were obtained from the baseline evaluation. All patients included were diagnosed according to UK PD Brain Bank criteria. Exclusion criteria were as follows: non-PD parkinsonism, dementia (Mini Mental State Examination (MMSE) < 26), age <18 or >75 years, inability to read or understand the questionnaires, to be receiving any advanced therapy (continuous infusion of levodopa or apomorphine and/or with deep brain stimulation), and the presence of comorbidity, sequelae, or any disorder that could interfere with the assessment.

Information on sociodemographic aspects, factors related to PD, comorbidity, and treatment was collected. Motor and NMS were evaluated using different validated scales [12]. In patients with motor fluctuations, the motor assessment (H&Y and UPDRS) was conducted during the OFF state (without medication in the last 12 hours; H&Y-OFF and UPDRS-III-OFF) and during the ON state (H&Y-ON and UPDRS-III-ON). However, in patients without motor fluctuations, it was only performed without medication (first thing in the morning without taking medication in the previous 12 hours). Moreover, in PD patients with motor fluctuations, the nonmotor assessment was conducted during the ON state [12]. The NMSS [7] was used for assessing NMS. This includes 30 items, each with a different nonmotor symptom. The symptoms refer to the 4 weeks prior to assessment. The total score for each item is the result of multiplying the frequency (0, never; 1, rarely; 2, often; 3, frequent; 4, very often) x severity (1, mild; 2, moderate; 3, severe) and will vary from 0 to 12 points. The scale score ranges from 0 to 360 points. The items are grouped into 9 different domains: (1) cardiovascular (items 1 and 2; score, 0 to 24); (2) sleep/fatigue (items 3, 4, 5, and 6; score, 0 to 48); (3) depression/apathy (items 7, 8, 9, 10, 11, and 12; score, 0 to 72); (4) perceptual problems/hallucinations (items 13, 14, and 15; score, 0 to 36); (5) attention/memory (items 16, 17, and 18; score, 0 to 36); (6) gastrointestinal tract (items 19, 20, and 21; score, 0 to 36); (7) urinary symptoms (items 22, 23, and 24; score, 0 to 36); (8) sexual dysfunction (items 25 and 26; score, 0 to 24); (9) miscellaneous (items 27, 28, 29, and 30; score, 0 to 48).

Three different instruments were used to assess QoL: (1) the PDQ-39 [14]; (2) a rating of global perceived Qol (PQ-10) on a scale from 0 (worst) to 10 (best) [8, 15]; and (3) the EUROHIS-QOL [16]. The PDQ-39 is a PD-specific questionnaire that assesses the patients’ health-related Qol. There are 39 items grouped into 8 domains: (1) mobility (items 1 to 10); (2) Activities of Daily Living (items 11 to 16); (3) emotional well-being (items 17 to 22); (4) stigma (items 23 to 26); (5) social support (items 27 to 29); (6) cognition (items 30 to 33); (7) communication (items 34 to 36); and (8) pain and discomfort (items 37 to 39). For each item, the score may range from 0 (never) to 4 (always). The symptoms refer to the 4 weeks prior to assessment. Domain total scores are expressed as a percentage of the corresponding maximum possible score, and a Summary Index is obtained as average of the domain scores. The EUROHIS-QOL is an 8-item global QoL questionnaire (quality of life, health status, energy, autonomy for Activities of Daily Living, self-esteem, social relationships, economic capacity, and habitat) derived from the WHOQOL-BREF. For each item, the score ranges from 0 (not at all) to 5 (completely). The total score is expressed as the mean of the individual scores. A higher score indicates a better QoL. The Schwab and England Activities of Daily Living Scale (ADLS) was used for assessing disability [17]. Functional dependency was defined as an ADLS score less than 80% (80% = completely independent; 70% = not completely independent) [18].

2.1. Data analysis. Data were processed using SPSS 20.0 for Windows. NMS burden was defined as follows: mild (NMSS 1-20); moderate (NMSS 21-40); severe (NMSS 41-70); and very severe (NMSS > 70) [10]. Each domain of the NMSS was expressed as a percentage: (score/total score) x 100. The patients were classified according to H&Y-OFF (1, stage I; 2, stage II; 3, stage III; 4, stage IV/V) and NMS burden (A: 0-20; B: 21-40; C: 41-70; D: ≥ 71) in 16 stages (HY.NMSB): 1A, 1B, 1C, 1D, 2A, 2B, 2C, 2D, 3A, 3B, 3C, 3D, 4A, 4B, 4C, and 4D. PDQ-39 was expressed as a Summary Index (PDQ-39SI): (score/156) x 100. For comparisons between patients with a different H&Y stage, NMS burden stage, and/or HY.NMSB stage, chi-squared, ANOVA, and/or Mann-Whitney–Wilcoxon test were applied. With the aim of determining if the HY.NMSB contributes to the patient’s QoL independently of other factors, a multiple regression analysis was conducted (PDQ-39SI as dependent variable). A p value ≤ 0.05 was considered significant.

2.2. Standard Protocol Approvals, Registrations, and Patient Consent. For this study, we received approval from the Comité de Ética de la Investigación Clínica de Galicia from Spain (2014/534; 02/DEC/2014). Written informed consents from all participants in this study were obtained before the start of the study. COPPADIS-2015 was classified by the AEMP (Agencia Española del Medicamento y Productos Sanitarios) as a postauthorization prospective follow-up study with the code COH-PAK-2014-01.
3. Results

A total of 603 PD patients (62.7 ± 8.9 years old; 59.5% males) from the COPPADIS cohort were included in the analysis. The mean disease duration was 5.7 ± 4.5 years. One-hundred and twenty-eight (22.9%) patients were in stage I of H&Y, 407 (67.5%) in stage II of H&Y, 49 (8.1%) in stage III of H&Y, and only 9 (1.5%) in stage IV/ V of H&Y. The mean NMSS total score was 46.7 ± 38.2, presenting 162 (26.9%) patients with mild NMS burden, 174 (28.8%) with moderate NMS burden, 140 (23.2%) with severe NMS burden, and 127 (21.1%) with very severe NMS burden. No patient presented absence of nonmotor symptoms (NMSS = 0). Data about PD-related variables are shown in Table SM 1. When H&Y and NMS burden were combined (HY.NMSB), a higher percentage of patients with severe or very severe NMS burden in advanced H&Y stages (III and/or IV/V) (p < 0.0001) was observed (Figure 1).

A worse QoL and a greater disability were associated with a higher H&Y stage. Specifically, the PDQ-39SI and the EUROHIS-QOL8 total score were significantly lower and higher, respectively, in patients with a lower H&Y (Table 1 and Figure 2(a)). The ADLS score was higher (indicative of lower disability) in patients with a lower H&Y (Table 1). When patients with a consecutive stage of H&Y were compared, the most significant differences were observed between patients with a stage II of H&Y and those ones with stage III, but no differences were observed between patients with a stage III of H&Y and those ones with stage IV (only 9 patients in this last subgroup) (Table 1). QoL and disability were related to NMS burden as well, so the higher the NMS burden stage, the worse the QoL, and the greater the disability (Table 2 and Figure 2(b)). After classifying participants by combining both scales, H&Y and NMSS (NMSS), QoL and disability were related to the HY.NMSB stage (Figure 2(c)): PDQ-39SI, from 6.7 ± 4.9 (HY.NMSB 1A) to 42.9 ± 11.9 (HY.NMSB 4D) (p < 0.0001); EUROHIS-QOL8 total score, from 4.1 ± 0.5 (HY.NMSB 1A) to 31.1 ± 0.6 (HY.NMSB 3D) (p < 0.0001; only 1 patient in the stage 4B but with a score of 4.5); and ADLS score, from 94.9 ± 5.7 (HY.NMSB 1A) to 55 ± 19.1 (HY.NMSB 4D) (p < 0.0001). With regard to our hypothesis, it was observed that patients with a lower stage of H&Y could have a worse QoL and/or a greater disability if they had a greater NMS burden (Tables 3 and 4). For example, patients with stage I of H&Y and very severe NMS burden (HY.NMSB 1D; n = 15) compared to patients with stage II of H&Y but mild NMS burden (HY.NMSB 2A; n = 101) had a higher PDQ-39SI (28.6 ± 17.1 vs 7.9 ± 5.8; p < 0.0001) and a lower ADLS score (6.4 ± 1.5 vs 7.9 ± 1.2; p < 0.0001), EUROHIS-QOL8 (3.5 ± 0.4 vs 4.1 ± 0.4; p < 0.0001), and ADLS score (88 ± 6.8 vs 91.8 ± 5.9; p = 0.025) (Table 3 and Figure 2). Even PDQ-39SI (198 ± 11.9 vs 138 ± 9.8; p = 0.003) and EUROHIS-QOL8 score (3.6 ± 0.5 vs 3.9 ± 0.5; p = 0.030), we are significantly higher and lower, respectively, in those patients with stage I of H&Y and severe NMS burden HY.NMSB 1C; n = 27) than those in ones with stage <II of H&Y and moderate NMS burden (HY.NMS 2B; n = 125) (Table 3 and Figure 2). When patients with a stage II of H&Y were compared with those ones with a stage III, a worse QoL was observed in patients with stage II and very severe NMS burden (HY.NMS 2D; n = 91) than those in patients with a stage III of H&Y but mild NMS burden (HY.NMS 3A; n = 6) or moderate NMS burden = (HY.NMS 3B; n = 9): PDQ-39SI 31.8 ± 3.8 vs 14.2 ± 10.9; p = 0.003; 31.8 ± 13.8 vs. 21.5 ± 7.9 (p = 0.029); PQ-10, 6.2 ± 1.6 vs 8.5 ± 1.5 (p = 0.003); EUROHIS-QOL8, 3.8 ± 0.6 vs 3.6 ± 0.4 (p = 0.048) (Table 4 and Figure 2).

In a simple linear regression model, the HY.NMSB scale predicted the PDQ-39SI: β = 0.480; CI 95%, 1.981 – 2.661; p < 0.0001. After adjustment to other covariates (age, gender, disease duration, levodopa equivalent daily dose, UPDRS-IV, FOGQ, and BDII), the HY.NMS stage contributed significantly to the patient’s QoL (PDQ-39SI as dependent variable) as well. Adjusted R-squared 0.591; β = 0.089; CI 95%, 0.098 – 0.770; p = 0.011 (Table 2. SM). As compared to the classical H&Y stage alone (not significant in the model), the HY.NMS was multiplied by 12.7 the size effect over the PDQ-39SI (β standardized coefficient of 0.007 for the H&Y in a model with age, gender, disease duration, levodopa equivalent daily dose, UPDRS-IV, FOGQ, BDII-I and, NMSS (p = 0.823) vs 0.089 for the HY.NMS in the model with the same covariates included except the NMSS (p = 0.011)).

4. Discussion

The present study observed that the use in PD patients of a scale that combines the H&Y stage with the NMSS (HY.NMSB) could be useful since it would not only inform about motor and nonmotor aspects but would also serve to know how is the patient’s QoL and autonomy for ADL. This is relevant because many PD patients can be in stages I to III of H&Y for many years and stratification regarding NMS burden providing useful information not only for diagnosis but also for monitoring the outcome and ideally the response to a medication.

Ray Chaudhuri et al. [11] proposed a new strategy for clinical classification of PD patients using the NMSS in 5 stratified levels of burden (0 = no NMS; 1 = NMSS, 1-20; 2 = NMSS, 21-40; 3 = NMSS, 41-70; 4 = NMSS > 70) and suggested that this simple assessment could be added to existing motor-based staging (i.e., H & Y) to complement PD assessment and avoid overlooking the weight of the NMS. In 951 PD patients, these authors observed a significant influence of NMS burden on disability and Qol, highlighting the need to include an NMS evaluation for a complete assessment of PD patients. We observed the same in 603 PD patients from the COPPADIS cohort. However, here, we define specifically a scale (HY.NMSB) combining the H&Y stage with the NMS burden: firstly, a number for the H&Y from 1 (stage I) to 4 (stage IV/V); secondly, a letter for the NMS burden from A (non NMS or mild NMS burden; NMSS 0-20) to D (very severe burden; NMSS > 70). Combining the number with the letter, a total of 16 stages are defined, from HY.NMSB 1A (H&Y I and non-NMS/mild NMS burden) to 4D (H&Y IV/V and very severe NMS burden). PD patients without NMS (i.e., NMSS total
score = 0) are rare (none in this cohort), but in any case, they are included as “A” because there is really no difference between, for example, a patient with NMSS total score = 0 and another one with NMSS total score = 1 or 3. So, “A” is defined as a patient without NMS or mild NMS burden. On the other hand and with the idea of simplifying the scale,
very advanced PD patients with regard to motor stage (H&Y IV and V) are considered together as number 4. After applying this scale (HY.NMSB) for the first time, we observed that QoL and disability were related to H&Y but NMS burden as well, so patients with a lower H&Y but a greater NMS burden can perceive a worse QoL and greater disability than patients with a higher H&Y stage but lower NMS burden. Conventionally, H&Y stages I and II represent mild

Table 2: Quality of life (PDQ-39SI and EUROHIS-QOL8) and disability (ADLS score) in PD patients with regard to nonmotor symptoms burden: mild (NMS total score 1-20); moderate (NMS total score 21-40); severe (NMS total score 41-70); very severe (NMS total score > 70).

|                  | Mild, N = 162 | Moderate, N = 174 | Severe, N = 140 | Very severe, N = 127 | \( p^a \) | \( p^b \) | \( p^c \) | \( p^d \) |
|------------------|---------------|-------------------|-----------------|----------------------|---------|---------|---------|---------|
| PDQ-39SI         | 7.7 ± 5.7     | 13.8 ± 9.7        | 19.9 ± 10.7     | 32.9 ± 14.4          | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Mobility         | 6.2 ± 11.5    | 12.7 ± 15.6       | 19.7 ± 15.9     | 35.3 ± 22.9          | <0.0001 | <0.0001 | 0.0029  | <0.0001 |
| Activities       | 9.5 ± 11.1    | 15.8 ± 15.4       | 19.8 ± 16.7     | 32.4 ± 23.3          | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Emotional        | 9.9 ± 10.8    | 15.6 ± 13.9       | 26.6 ± 18.7     | 41.6 ± 22.6          | <0.0001 | 0.001   | 0.149   | <0.0001 |
| Stigma           | 7.6 ± 14.1    | 13.7 ± 18.9       | 10.8 ± 16.2     | 22.9 ± 25.5          | <0.0001 | 0.025   | 0.001   | <0.0001 |
| Social support   | 2.2 ± 8.9     | 4.9 ± 12.8        | 10.6 ± 17.5     | 18.6 ± 21.9          | <0.0001 | <0.0001 | <0.0001 | 0.001   |
| Cognition        | 7.2 ± 9.6     | 16.2 ± 13.9       | 24.6 ± 16.2     | 34.9 ± 20.1          | <0.0001 | <0.0001 | 0.036   | <0.0001 |
| Communication    | 3.5 ± 7.3     | 8.3 ± 12.4        | 11.6 ± 14.7     | 19.3 ± 19.7          | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Pain and         | 14.7 ± 15.6   | 20.7 ± 18.9       | 30.7 ± 19.6     | 47.4 ± 24.8          | <0.0001 | 0.002   | <0.0001 | <0.0001 |
| discomfort        |               |                   |                 |                      |         |         |         |         |
| PQ-10            | 7.9 ± 1.2     | 7.5 ± 1.4         | 6.9 ± 1.4       | 6.1 ± 1.7            | <0.0001 | <0.0001 | <0.0003 | <0.0001 |
| EUROHIS-QOL8     | 4.1 ± 0.5     | 3.9 ± 0.4         | 3.6 ± 0.5       | 3.3 ± 0.6            | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Quality of life   | 4.1 ± 0.5     | 3.9 ± 0.6         | 3.7 ± 0.7       | 3.3 ± 0.8            | <0.0001 | 0.005   | <0.0001 | <0.0001 |
| Health status    | 3.5 ± 0.8     | 3.3 ± 0.8         | 3 ± 0.8         | 2.6 ± 0.9            | <0.0001 | 0.001   | 0.006   | <0.0001 |
| Energy           | 4.2 ± 0.7     | 3.8 ± 0.7         | 3.6 ± 0.8       | 3.2 ± 0.9            | <0.0001 | <0.0001 | 0.004   | <0.0001 |
| Autonomy for ADL | 4 ± 0.7       | 3.8 ± 0.8         | 3.4 ± 0.8       | 3 ± 0.9              | <0.0001 | 0.001   | <0.0001 | <0.0001 |
| Self-esteem      | 4.2 ± 0.6     | 3.9 ± 0.7         | 3.6 ± 0.7       | 3.3 ± 0.9            | <0.0001 | 0.010   | <0.0001 | <0.0001 |
| Social           | 4.4 ± 0.6     | 4.1 ± 0.6         | 3.9 ± 0.7       | 3.6 ± 0.8            | <0.0001 | <0.0001 | 0.059   | <0.0001 |
| Economic         | 4.1 ± 0.8     | 3.9 ± 0.7         | 3.8 ± 0.7       | 3.5 ± 0.9            | <0.0001 | 0.079   | 0.180   | 0.001   |
| Habitat          | 4.4 ± 0.7     | 4.3 ± 0.6         | 4.2 ± 0.7       | 3.9 ± 0.7            | <0.0001 | 0.105   | 0.123   | 0.011   |
| ADLS score       | 92.9 ± 6.1    | 90.2 ± 8.3        | 86.5 ± 10.4     | 80.5 ± 12.9          | <0.0001 | 0.001   | <0.0001 | <0.0001 |
| Functional       |               |                   |                 |                      |         |         |         |         |
| dependency (%)   | 0.6           | 4.6               | 11.5            | 28.3                 | <0.0001 | 0.024   | 0.019   | <0.0001 |
Table 3: Quality of life (PDQ-39SI and EUROHIS-QOL8) and disability (ADLS score) in patients with stages 1C, 1D, 2A, or 2B of the HY-NMSB scale.

| Stage | PDQ-39SI | Mobility | Activities of Daily Living | Emotional well-being | Stigma | Social support | Cognition | Communication | Pain and discomfort | PQ-10 | EUROHIS-QOL8 | Quality of life | Health status | Energy | Autonomy for ADL | Self-esteem | Social relationships | Economic capacity | Habitat | ADLS score | FD (%) |
|-------|----------|----------|-----------------------------|----------------------|--------|----------------|-----------|---------------|---------------------|-------|----------------|----------------|----------------|--------|----------------|-------------|------------------|----------------|--------|-------------|--------|
| 1C, N = 27 | 19.8 ± 11.9 | 18.1 ± 14.9 | 16.5 ± 15.2 | 28.7 ± 16.4 | 16.4 ± 20.4 | 13.6 ± 17.8 | 21.9 ± 17.4 | 14.2 ± 15.9 | 27.8 ± 20.1 | 6.9 ± 1.6 | 3.6 ± 0.5 | 3.6 ± 0.6 | 3.2 ± 0.9 | 3.4 ± 0.7 | 3.5 ± 0.7 | 3.6 ± 0.8 | 3.9 ± 0.6 | 3.7 ± 0.7 | 3.9 ± 0.8 | 92.6 ± 7.1 | 0.0 ± 0.0 |
| 1D, N = 15 | 28.6 ± 17.1 | 27.8 ± 17.7 | 28.3 ± 18.3 | 35.5 ± 21.3 | 23.8 ± 23.9 | 19.4 ± 22.6 | 32.5 ± 18.8 | 20.6 ± 19.6 | 38.3 ± 27.4 | 6.4 ± 1.5 | 3.5 ± 0.4 | 3.2 ± 0.6 | 3.2 ± 0.6 | 3.4 ± 0.6 | 3.5 ± 0.5 | 3.5 ± 0.5 | 3.8 ± 0.6 | 3.4 ± 0.7 | 3.9 ± 0.7 | 88.6 ± 6.8 | 1 |
| 2A, N = 101 | 7.9 ± 5.8 | 6.1 ± 10.5 | 10.9 ± 12.4 | 8.9 ± 9.4 | 8.4 ± 15.7 | 2.4 ± 9.9 | 8.3 ± 9.6 | 4.1 ± 8.4 | 13.5 ± 13.5 | 7.9 ± 1.2 | 4.1 ± 0.4 | 4.1 ± 0.6 | 3.6 ± 0.7 | 4.1 ± 0.6 | 4.1 ± 0.6 | 4.2 ± 0.6 | 4.4 ± 0.6 | 3.8 ± 0.7 | 4.1 ± 0.6 | 91.8 ± 5.9 | 1 |
| 2B, N = 125 | 13.8 ± 9.8 | 13 ± 16.2 | 15.9 ± 16.1 | 14.9 ± 13.7 | 13.9 ± 19.9 | 5.3 ± 13.8 | 15.9 ± 13.7 | 7.9 ± 12.1 | 21.2 ± 20.3 | 7.5 ± 1.5 | 3.9 ± 0.5 | 3.9 ± 0.6 | 3.3 ± 0.8 | 3.8 ± 0.7 | 3.7 ± 0.7 | 3.9 ± 0.7 | 4.2 ± 0.6 | 3.9 ± 0.6 | 6.4 ± 0.6 | 89.5 ± 8 | 4 |

Chi-squared and Mann–Whitney–Wilcoxon test were applied. The results represent means or mean ± SD; p < 0.01 vs 2A; p < 0.02 vs 2B; p < 0.05 vs 1C; p < 0.06 vs 2C; p < 0.07 vs 2B vs 2C; p < 0.08 vs 1B, 2B; Schwab and England Activities of Daily Living Scale; EUROHIS-QOL8, EUROHIS-QOL 8-item index; PDQ-39SI, 39-item Parkinson’s Disease Quality of Life Questionnaire Summary Index.

Table 4: Quality of life (PDQ-39SI and EUROHIS-QOL8) and disability (ADLS score) in patients with stages 2C, 2D, 3A, or 3B of the HY-NMSB scale.

| Stage | PDQ-39SI | Mobility | Activities of Daily Living | Emotional well-being | Stigma | Social support | Cognition | Communication | Pain and discomfort | PQ-10 | EUROHIS-QOL8 | Quality of life | Health status | Energy | Autonomy for ADL | Self-esteem | Social relationships | Economic capacity | Habitat | ADLS score | FD (%) |
|-------|----------|----------|-----------------------------|----------------------|--------|----------------|-----------|---------------|---------------------|-------|----------------|----------------|----------------|--------|----------------|-------------|------------------|----------------|--------|-------------|--------|
| 2C, N = 93 | 18.5 ± 10.2 | 17.2 ± 14.9 | 18.4 ± 16.4 | 25.6 ± 20.1 | 9.3 ± 15.1 | 9.9 ± 16.7 | 24.4 ± 15.9 | 9.5 ± 13.6 | 30.9 ± 19.6 | 7.1 ± 1.4 | 3.7 ± 0.4 | 3.7 ± 0.7 | 3.7 ± 0.7 | 3.7 ± 0.7 | 3.7 ± 0.7 | 3.7 ± 0.7 | 3.7 ± 0.7 | 3.7 ± 0.7 | 24.4 ± 24.6 | 21.2 ± 26.6 | 28.7 ± 19.6 | 0.003 | 0.003 |
| 2D, N = 91 | 31.8 ± 13.8 | 32 ± 2.1 | 31.1 ± 23.3 | 41.7 ± 23.1 | 22.4 ± 24.4 | 19.1 ± 21.9 | 35.7 ± 21.2 | 18.4 ± 18.7 | 46.1 ± 24.6 | 6.2 ± 1.6 | 3.3 ± 0.6 | 3.4 ± 0.7 | 2.6 ± 0.9 | 3.2 ± 0.9 | 3.2 ± 0.9 | 3.2 ± 0.9 | 3.2 ± 0.9 | 3.2 ± 0.9 | 6.8 ± 8.6 | 2.6 ± 6.8 | 13.9 ± 13.8 | 0.025 | 0.025 |
| 3A, N = 6 | 14.2 ± 10.9 | 27.1 ± 31.2 | 6.9 ± 7.7 | 15.9 ± 20.8 | 7.3 ± 15 | 0 ± 0 | 1 ± 2.6 | 2.8 ± 6.8 | 34.7 ± 22.6 | 8.5 ± 1.5 | 3.6 ± 0.6 | 4 ± 0.9 | 3.2 ± 0.7 | 3.8 ± 0.4 | 3.8 ± 0.4 | 3.8 ± 0.4 | 3.8 ± 0.4 | 3.8 ± 0.4 | 13 ± 18.7 | 7.2 ± 13.3 | 24.3 ± 13.4 | <0.0001 | <0.0001 |
| 3B, N = 9 | 21.5 ± 7.9 | 27.5 ± 16.3 | 25.9 ± 11.7 | 24.5 ± 19.5 | 6.9 ± 14.1 | 2.8 ± 4.2 | 24.3 ± 13.4 | 13.9 ± 13.8 | 28.7 ± 19.6 | 7.2 ± 1.3 | 3.6 ± 0.4 | 3.6 ± 0.5 | 2.7 ± 0.5 | 3.6 ± 0.5 | 3.6 ± 0.5 | 3.6 ± 0.5 | 3.6 ± 0.5 | 3.6 ± 0.5 | 8.6 ± 8.6 | 0.28 ± 0.1 | <0.0001 | <0.0001 |

Chi-squared and Mann–Whitney–Wilcoxon test were applied. The results represent means or mean ± SD; p < 0.01 vs 2A; p < 0.02 vs 2B; p < 0.05 vs 1C; p < 0.06 vs 2C; vs 3B; Schwab and England Activities of Daily Living Scale; EUROHIS-QOL8, EUROHIS-QOL 8-item index; PDQ-39SI, 39-item Parkinson’s Disease Quality of Life Questionnaire Summary Index.

PD, but this qualification cannot be supported attending the load of NMS and any domain/s they belong. The NMS present in PD may be very variable in number and type, and they maintain only a moderate association with the motor disturbances [10, 11, 19, 20]. In fact, although as expected, patients with mild NMS burden (A; 39.8%) were the most frequent in the group with a stage I of H&Y and patients with very severe NMS burden (D; 44.4%) in the group with H&Y IV/V; more than 30% of the patients in stage I of H&Y had severe or very severe NMS burden. Clinical and
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neuropathological data are now emerging supporting the concept of the nonmotor dominant endophenotype [21], and it seems necessary in daily practice to know the frequency and the severity of NMS in PD patients, even in early PD patients, because NMS burden could be significant, and this one impacts on their QoL and contributes to disability [7, 9, 15, 22]. Very recently, two PD subtypes have been suggested [23, 24], and it would be of great interest to know if very early PD patients with very severe NMS burden could correspond with the body-first (bottom-up) type and those with mild NMS burden with the brain-first (top-down) type.

The application of the HY.NMSS scale could have different uses: (1) a fast and relatively simple way of knowing the motor and nonmotor states of a PD patient, stratifying him/her into a group (diagnosis value; first visit); (2) to monitor the long-term evolution of the patient (prognosis value; follow-up visits); (3) to monitor the response of a patient to a specific therapeutic intervention. In fact, the NMSS total score has been considered as the primary efficacy variable in recent trials [25], and it is known that some NMS can be improved, with dopaminergic medication or nondopaminergic medication [26]. In this context, the HY.NMSS could be used for defining a specific population or as an outcome parameter in clinical trials. For example, nabilone has very recently demonstrated to improve NMS in PD patients in a phase 2 trial [27], being an interesting possibility to identify what patients changed from a superior stage of the HY.NMSS to an inferior stage (e.g., from 2C to 2 B). Finally, the HY-NMSS scale could be useful to indirectly estimate the patient’s perception of QoL and disability. The correlation of H&Y, NMSS, and NMS burden with QoL and disability has been frequently reported [7–9, 22], including in PD patients from the COPPADIS cohort [15, 18], but this is the first time that the relationship considering both motor stage (H&Y) and NMS burden (NMSS) at the same time has been analyzed, and it is important because the influence of NMS burden on QoL perception is critical. An inherent limitation of the proposed classification (HY.NMSS) is the fact that the classification according to NMS is carried out taking into account the total NMS burden but without considering what exactly these symptoms are. Importantly, some NMS could help clinical practitioners to identify patients who are at different stages of the disease, such as hallucinations, fainting, inability to control body sphincters, or believing in unlikely facts [28]. Moreover, and compared with the International Parkinson and Movement Disorder Society—Nonmotor Rating Scale (MDS-NMS) [29], the NMSS collects the patient’s perception about different NMS in the previous 4 weeks but does not about nonmotor fluctuations.

A very important limitation is that our sample is not fully representative of the PD population due to inclusion and exclusion criteria (i.e., age limit, no dementia, no severe comorbidities, and no second line therapies) which subsequently entails a bias toward early PD. The majority of the patients from this cohort were in the stage I or II of the H&Y (90.4%), so the same analysis with the proposed classification should be carried out in a cohort with more patients in advanced stages of H&Y. In spite of this and importantly, during the first 5 to 10 years of the disease, many patients with PD will be in stage II of the H&Y, and introducing the NMS burden will help to differentiate the degree of nonmotor affection, that importantly correlates with QoL perception. In other words, the results of the present study are applicable for a long time to the majority of PD patients, especially in early young PD patients. Second, all scales or questionnaires used for assessing motor and NMS are validated except PQ-10 [8, 15]. Third, NMS were recorded with the NMSS, but specifically, as we commented nonmotor fluctuations were not identified [30]. Fourth, the OFF state (12 hours without taking medication) was considered for defining the H&Y stage because it represents a more natural state of the disease less conditioned by the symptomatic effect of the medication. Moreover, in PD patients with motor fluctuations, the symptoms during the OFF state mostly impact on QoL and autonomy. In any case, previously, similar results applying the HY.NMSS were observed when the H&Y stage was defined during the ON state in 149 PD patients from the CASINO cohort [8, 31]. In the COPPADIS cohort, the results were similar as well when the H&Y was defined during the ON state in those PD patients with motor fluctuations (data not shown). Fifth, the time it took to administer the HY.NMSS scale was not calculated. Finally, this is a cross-sectional study, but the aim of the COPPADIS-2015 study [12] is to follow-up the cohort for 5 years, so changes in HY.NMSS and the relationship with changes in other variables could be analyzed.

In conclusion, this is the first time that a specific scale combing the H&Y stage and the NMSS (HY.NMSS scale) is applied in PD patients for knowing the relationship with the patient’s QoL perception and disability regarding the stage. The HY.NMSS scale is simple and reflects the degree of patient involvement more accurately than the H&Y. Patients with a lower H&Y stage may be more affected if they have a greater NMS burden. These results need to be replicated in a larger and well-distributed cohort of patients by motor stage.

Appendix

A. COPPADIS Study Group

The authors in the COPPADIS Study Group have been listed in Table 5.

Abbreviations

ADLS: Schwab and England Activities of Daily Living Scale
BDI: Beck depression inventory-II
EUROHIS-QOL8: European Health Interview Survey-Quality of Life 8 Item-Index
FOGQ: Freezing of gait questionnaire
H&Y: Hoehn and Yahr
NMS: Nonmotor symptoms
NMSB: Nonmotor symptoms burden
NMSS: Nonmotor symptoms scale
NPI: Neuropsychiatric inventory
PD: Parkinson’s disease
PD-CRS: Parkinson’s Disease Cognitive Rating Scale
PDQ-39SI: 39-Item Parkinson’s Disease Quality of Life Questionnaire Summary Index
PDSS: Parkinson’s Disease Sleep Scale
QoL: Quality of life
QUIP-RS: Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease Rating Scale
UPDRS: Unified Parkinson’s Disease Rating Scale
VAFS: Visual Analog Fatigue Scale
VAS pain: Visual Analog Scale Pain.

Data Availability

The protocol and the statistical analysis plan are available on request. Deidentified participants data are not available for legal and ethical reasons.

Conflicts of Interest

Santos García D has received honoraria for educational presentations and advice service by AbbVie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, Italfarmaco, and Teva. Paz González JM has received honoraria for educational presentations and/or advice service by UCB Pharma, Lundbeck, KRKA, and Zambon. Jesús S has received honoraria from AbbVie, Bial, Merz, UC, and Zambon and holds the competitive contract “Juan Rodés” supported by the Instituto de Salud Carlos III. She has received grants from the Spanish Ministry of Economy and Competitiveness (PI18/01898) and the Consejería de Salud de la Junta de Andalucía (PI-0459-2018). Aguilar M obtained from UCB and Schwabe with assistance to a Congress and Nutricia with assistance to a Congress and payment of lecture. Planellas LL has received travel bursaries grant from AbbVie. García Caldentey J has received honoraria for educational presentations and advice service by Qualigen, Nutricia, AbbVie, Italfarmaco, UCB Pharma, Lundbeck, Zambon, Bial, and Teva. Caballol N has received honoraria from Bial, Italfarmaco, Qualigen, Zambon, UCB, Teva, and KRKA and sponsorship from Zambon, TEVA, and AbbVie for attending medical conferences. Legarda I has received honoraria for educational presentations and advice service by AbbVie, UCB Pharma, Zambon, Bial, and Teva. Hernández Vara J has received travel bursaries and educational grants from AbbVie and has received honoraria for educational presentations from AbbVie, Teva, Bial, Zambon, Italfarmaco, and Sanofi-Genzyme. Cabo I has received honoraria for educational presentations and advice service by AbbVie, Zambon, and Bial. López Manzanares L compensated advisory services, consulting, research grant support, or speaker honoraria from AbbVie, Acorda, Bial, Intec Pharma, Italfarmaco, Pfizer, Roche, Teva, UCB, and Zambon. Ávila Rivera MA has received honoraria from Zambon, UCB Pharma, Qualigen, Bial, and Teva and ana sponsorship from Zambon and Teva for attending conferences.

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Authors’ Contributions
Santos García D was responsible for conception, organization, and execution of the project; statistical analysis; writing of the first draft of the manuscript; and recruitment and/or evaluation of participants. De Deus T Suárez E, Jesús S Aguilar M, Pastor P, Planellas LL, Cosgaya M, García Caldentey J, Caballol N, Legarda I, Hernández Vará J, Cabo I, López Manzanares L, González Aramburu I, Ávila Rivera MA, Catalán MJ, Nogueira V, Puente V, García Moreno JM, Borrué C, Solano Vila B, Álvarez Sauco M, Vela L, Escalante S, Cubo E, Carrillo Padilla F, Martínez Castrillo JC, Sánchez Alonso P, Alonso Losada MG, López Ariztegui N, Gastón I, Kulishevsky J, Blázquez Estrada M, Seijo M, Ruiz Martínez J, Valero C, Kurtis M, de Fábregues O, González Ardura J, Ordás C, López Díaz L, and Mir P contributed to review and critique and recruitment and/or evaluation of participants. Paz González JM, Cores Bartolomé C, Valdés Aymerich L, and Muñoz Enríquez JG managed review and critique. Martínez-Martin P did review and critique and supervision.

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Supplementary Materials
Table 1 SM. Disease-related characteristics, motor and nonmotor symptoms, and autonomy for activities of daily living and quality of life in PD patients (n=603). Table 2 SM. Multiple regression model for PDQ-39SI as dependent variable. (Supplementary Materials)

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