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Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale

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ABSTRACT

Background: Severity of PD is usually assessed by means of the motor and disability-based Hoehn and Yahr staging (HY), or clinician and patient global perceptions. Scores of more detailed assessments, as the MDS-UPDRS, have not been translated to a grading that allows assignment of score sections to severity levels. The objective of the present study is to determine cut-off points for PD severity levels based on the MDS-UPDRS.

Methods: International, observational study. Applied assessments were: HY, MDS-UPDRS, Clinical Impression for Severity Index, and Clinical and Patient Global Impression of Severity. The coincidence in severity level (mild, moderate, severe) of at least two clinical classifications plus the patient's gradation was considered "the criterion of severity". Cut-off values for each MDS-UPDRS subscale was determined by triangulation of: 1) percentile 90 of the subscale total score; 2) receiver operating characteristic (ROC) analysis; and 3) ordinal logistic regression (OLR) model.

Results: Sample was composed of 452 consecutive PD patients without dementia, 55.3% males, age 65.1 ± 10.7 years and PD duration 8.7 ± 6.3 years. All HY stages were represented. The "criterion", classified 275 patients (60.8% of the sample) as: mild PD, 149 (54.2%); moderate, 82 (29.8%); and severe, 44 (16%). The following MDS-UPDRS cut-off points between mild/moderate and moderate/severe levels were found: Part 1: 10/11 and 21/22; Part 2: 12/13 and 29/30; Part 3: 32/33 and 58/59; and Part 4: 4/5 and 12/13.

Conclusion: Cut-off points to classify PD patients as mild, moderate, or severe on the basis of their MDS-UPDRS scores are proposed.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that clinically evolves over time from subtle non-specific

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non-motor manifestations of the premotor phase to the most advanced stages in which patients are severely disabled. Progressive disability is due to the combination of motor and non-motor problems and related complications that increase in number and severity throughout the course of the disease making the clinical management more complex and affecting patients' quality of life and independence [1–3].

Since the publication of the Hoehn and Yahr staging [4], measures to evaluate PD have evolved to comprehensive evaluations as, for example, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [5] and the Non-Motor Symptoms Scale [6] or to assessments focused on a specific aspect such as the Parkinson's Fatigue Scale [7] and the Parkinson's Disease Dyskinesia Scale [8], among others. However, with the increasing complexity of the disorder there is an increased difficulty to determine the severity of the disease in a pragmatic and easily understandable manner [9] and a combination of several global self-reported and administered scales may be needed to approach this objective.

Global measures have the advantage of providing concise information on the overall health state and can be useful for patients selection (for example, cases with "mild disease" for a clinical trial) and classification (for example, assignment of a "very dependent" level for receiving social assistance). In short, the distribution of patients in such categories as mild, moderate, and severe, helps to determine in a pragmatic manner their global health status, facilitates the communication, and allows the decision making process.

The most frequently used global assessment for PD is the Hoehn and Yahr staging (HY) [4,10]. It is based on the disability resulting from motor impairment and balance dysfunction, but does not inform about some motor features and non-motor manifestations. It is widely used for description of PD patients groups and case selection for studies.

The generic Clinical Global Impression (CGI) [11] is a global measure mainly applied in psychiatry, but also used in PD as an outcome into clinical trials and other kind of studies. The CGI has two main components, respectively focused on severity (CGIS) and change (CGIC). The CGI has been criticized as inconsistent and too general [12], but is widely used. The CGIS can be adapted for patients self-assessment (PGIS), a strategy allowing comparisons between rater-based and patient-based evaluation [12].

A recent approach to global evaluation of PD is the Clinical Impression of Severity Index for PD (CISI-PD), a specific instrument based on the global clinical impression on four relevant aspects of PD: motors signs, disability, motor complications, and cognitive impairment, a combination that explained 92% of the CGIS variance [13]. The CISI-PD summarizes the evaluation carried out through the interview, examination, and application of other assessments.

The present study was aimed at determining, using agreed levels of severity among these professional- and patient-based generic scales, the cut-off points for the MDS-UPDRS subscales that could determine levels of disease severity of useful clinical application.

2. Methods

2.1. Design

Multicenter, international, observational, cross-sectional study.

2.2. Patients

Consecutive patients with diagnosis of PD by a neurologist with expertise in movement disorders, according to international criteria [14], were recruited. Patients suffering for other chronic disabling conditions impeding or interfering with the evaluation of PD impact were excluded from the study. Patients unable to directly answering written questionnaires were helped by a trained person out of the patient's relationships and of the usual health professionals attending them. Patients with moderate or severe cognitive deterioration, according to MDS-UPDRS Part I – item 1 equal or greater than 3 and CISI-PD Cognition 4 or higher, were not included in the analysis.

Each participant site obtained approval from the local Ethics Committee or Institutional Review Board and patients had to give their signed consent to participate in the study.

2.3. Assessments

In addition to demographic and PD historical information, the following assessments were applied:

MDS-UPDRS Spanish version [5,15], a comprehensive scale composed of four parts: Part I – Non-Motor Experiences of Daily Living, which includes thirteen items: six rater-based and seven for patient self-assessment; Part II – Motor experiences of daily living, with 13 patient-based items; Part III – Motor examination, including 18 items (33 scores); and Part IV – Motor complications, formed of six items on dyskinesia and fluctuations. Each item scores from 0 (normal) to 4 (severe) and for each part, total scores are obtained from the sum of the corresponding item scores.

HY original version, that classifies the course of PD in five stages [4,10].

CISI-PD [13,16], an instrument that provides a clinical estimate of PD severity based on four outstanding PD aspects: motor signs, disability, motor complications, and cognitive status. Each domain scores from 0 (normal) to 6 (very severe) and the total score ranges from 0 to 24 points.

Global Impression of Severity. The 7-option clinician-based (CGIS) [11] and a 6-option patient-based global impression of severity (PGIS, with the option "severe" representing the collapse of the "markedly ill" and "severely ill"options that may be difficult to differentiate for patients) were included in the respective case report forms.

2.4. Data analysis

Descriptive statistics (central tendency and dispersion measures; proportions) were applied to characterize the variables in the sample. Levodopa-equivalent daily dose was calculated according to Tomlinson et al., 2010 [17].

Concordance among the four global evaluations was estimated by means of the Kendall's coefficient of concordance. Given the different structure of the four scales, a value $\geq$0.60 was considered satisfactory. Percentage of agreement between the scales was also determined.

The global evaluations were transformed to three severity categories – mild, moderate, and severe – according to previous studies or response options wording: HY classification (stages 1 and 2, mild; stage 3, moderate; and stages 4 and 5, severe) [10]; CISI-PD (1–7, mild; 8–14, moderate; $\geq$15, severe) [16]; CGIS (2–3, mild; 4, moderate; 5–7, severe); and PGIS (1–2, mild; 3, moderate; 4–5, severe) (Table 1).

The coincidence in degree of severity of at least two of the three clinical classifications plus the patient's gradation was adopted as "the criterion of severity" for this study. Comparison between groups broken down by these severity levels was carried out with the Kruskal–Wallis test. Bonferroni correction for multiple comparisons was applied.

Cut-off values for each MDS-UPDRS subscale by each severity level were determined by means of: 1) percentile 90 of the subscale total score; 2) receiver operating characteristic (ROC) analysis; and 3) ordinal logistic regression (OLR) model, calculating the probability curves for each category of severity and the cut-off points between these curves. The OLR was applied to ascertain the relationship between a continuous variable independent (the MDS-UPDRS subscales) and a dependent variable of ordinal type (the severity levels classification), allowing to obtain the cut-off points of the independent variable model logit associated with the '*k*' (three, in the present study) categories of the dependent variable. As foreseeably the three described methods would not coincide in their results, a triangulation by average of the three corresponding values was planned to estimate the value most probably close to the true cut-off point for each situation.

3. Results

The sample for the present study, from 9 different centres of seven countries, was composed of 452 patients, 55.3% males, with age (mean ± SD) 65.1 ± 10.7 years (range: 22–91) and PD duration 8.7 ± 6.3 years (range: 0–40). HY staging was: 69 (15.3%) were in stage 1; 163 (36.0%) in stage 2; 133 (29.4%) in stage 3; 70 (15.5%) in stage 4; and 17 (3.8%) in stage 5. Additional characteristics of the sample are shown in Table 2.

Concerning treatment for PD, 86.5% of patients received levodopa, 57.5% dopamine agonists, 49% a combination of both; and 36.6% other anti-PD drugs such as MAOB inhibitors or amantadine. Thirty-eight patients (8.4%) underwent functional surgery for PD.

Table 3 shows the distribution of the sample broken down by the PD severity levels (mild, moderate, severe) derived from the HY, CISI-PD, CGIS, and PGIS as described in the Data analysis section.