Parkinsonism and Related Disorders 25 (2016) 39–44

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Evaluation of severity of predominantly non-dopaminergic symptoms in Parkinson's disease: The SENS-PD scale

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ARTICLE INFO

Article history:
Received 24 November 2015
Received in revised form
11 February 2016
Accepted 16 February 2016

Keywords:
Parkinson's disease
Severity
Progression
Non-dopaminergic symptoms

ABSTRACT

Introduction: In spite of the multisystem nature of Parkinson's disease (PD), the formal assessment of its impairments is focused on symptoms predominantly reflecting degeneration of dopaminergic neurons. The aim of this study was to develop a valid and reliable rating scale of predominantly non-dopaminergic (PND) symptoms, which can be used as an additional measure of severity and progression of PD.
Methods: Using data of the PROPARK (N = 396) and ELEP (N = 365) cohorts, three items were selected from each of six selected PND domains (cognitive impairment, depressive symptoms, excessive daytime sleepiness, psychotic symptoms, autonomic dysfunction and Postural-Instability-and-Gait-Difficulty), based on item–total correlations. Hereafter, we evaluated reliability and validity of the resulting scale.
Results: The 18-item PND scale showed to be reliable and valid. Cronbach's alpha was 0.83. Principal component analysis using the six domain scores resulted in one factor, justifying the calculation of a sum score. Correlation coefficients of the sum score with severity of non-motor symptoms (non-motor part of MDS–UPDRS), motor symptoms (SPES/SCOPA scale), and Hoehn and Yahr stage were 0.63, 0.41 and 0.48, respectively ($p < 0.001$).
Conclusion: We developed a short, reliable and valid scale to evaluate severity of PND symptoms in PD. The score is expected to be largely insensitive to dopaminergic effects and may therefore more accurately reflect severity and progression of the underlying disease than currently used dopamine-sensitive measures. In combination with assessment of predominantly dopaminergic (motor) symptoms, a broad yet concise evaluation of PD is obtained, which better captures the widespread clinical consequences of the multisystem disease.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder involving dopaminergic and non-dopaminergic neurons [1]. In spite of the multisystem nature of PD, the evaluation of its impairments is focused on predominantly dopaminergic (motor) features. It is therefore expected that an assessment of symptoms which predominantly reflect degeneration of both dopaminergic and non-dopaminergic symptoms better captures the essence of the multi-system nature of PD [2]. Since predominantly non-dopaminergic (PND) symptoms are not, or only to a limited extent, confounded by the symptomatic effects of dopaminergic medication, their evaluation additionally provides a more accurate reflection of the actual clinical progression of PD.

For assessment of motor symptoms many instruments have been developed, of which the motor section of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS–UPDRS) [3] currently is the most widely used. For assessment of non-motor symptoms in PD two valid instruments are available: the non-motor part of the MDS–UPDRS and the Non-Motor Symptoms Scale (NMSS) [4]. These instruments differ in structure and content. The non-motor part of the MDS–UPDRS is used to identify areas in which patients may have problems, but does not provide detailed information on the assessed features. The NMSS is developed from an item pool and the number of items in the various domains is different, resulting in an unequal representation of the domains in the total score. In addition, the

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http://dx.doi.org/10.1016/j.parkreldis.2016.02.016
1353-8020/

consistency of the relation between the different domains over the course of PD is unknown. We therefore set out to develop a balanced clinical scaling system for the PND-axis, consisting of coherent symptoms that are already present in early disease and worsen with disease progression, and that is relatively unresponsive to dopaminergic medication.

Using factor analysis, a previous study identified a coherent pattern of six PND domains (Postural-Instability-and-Gait-Difficulty [PIGD], cognitive impairment, depressive symptoms, psychotic symptoms, excessive daytime sleepiness [EDS], and autonomic dysfunction) from a large pool of motor and non-motor symptoms reflecting the full spectrum of PD [5]. Subsequently it was shown that a composite score of this PND-complex robustly reflected disease severity and progression of PD [2]. However, the PND-complex is composed of 51 items from six different scales, which is unpractical for clinical practice.

In this study we aimed to develop a new reliable and valid multi-domain scale covering the relevant PND domains, the SEverity of Non-dopaminergic Symptoms in Parkinson's Disease (SENS-PD) scale, which accurately reflects disease severity and its progression, and is easy to administer in routine clinical practice of patients with PD.

2. Methods

2.1. PROPARK and ELEP study

The study is part of the "PROfiling PARKinson's disease" (PROPARK) study, a longitudinal cohort study of patients with PD. Data obtained from the baseline evaluation were used for analysis. Reproducibility of results was evaluated in data of the fourth annual evaluation of the PROPARK cohort and baseline evaluation of the 'Estudio Longitudinal de pacientes con Enfermedad de Parkinson' (ELEP) cohort.

2.2. Participants

All patients fulfilled established clinical diagnostic criteria for idiopathic PD [6]. Recruitment procedures of the PROPARK and ELEP cohorts have been described elsewhere [7,8]. The PROPARK study was approved by the medical ethics committee of the Leiden University Medical Center and the ELEP study by the Clinical Research Ethics Committees of the Carlos III Institute of Health and the Hospital de la Princessa, Madrid. Written informed consent was obtained from all participants. Patients who underwent stereotactic surgery were excluded from analysis.

2.3. Outcome measures

Within both cohorts all patients received standardized assessments. In the current study, six PND domains that were selected in earlier research were used for analysis [2]: PIGD (items 'rise from chair', 'postural instability' and 'gait' of the Short Parkinson's Evaluation Scale/Scales for Outcomes in Parkinson's Disease (SPES/SCOPA) [9]); psychotic symptoms (SCOPA–PC [10], items 1–5); EDS (SCOPA–SLEEP [11], section on daytime sleepiness); autonomic dysfunction (SCOPA–AUT [12], subdomains constipation [items 4–6], urinary function [items 8–13] and cardiovascular function [items 14–16]); cognitive impairment (SCOPA–COG [13]); and depressive symptoms (Hospital Anxiety and Depression Scale (HADS) [14], subscale depression). Higher scores reflect more severe impairment, except for the SCOPA–COG; for comparability, these item scores were reversed.

In addition, data on disease severity (Hoehn and Yahr stage (H&Y) [15], SPES/SCOPA motor score), age and disease duration (based on onset of first symptoms) were also collected. The SPES/SCOPA, SCOPA–PC, SCOPA–COG and H&Y were administered by trained research associates, whereas the SCOPA–AUT, SCOPA–SLEEP and HADS were self-completed by patients. For each patient, a levodopa dose equivalent (LDE) was calculated [16].

2.4. Analyses

The PIGD domain has the fewest items (i.e. 3). Therefore, 3 items were selected from each of the other PND domains, based on highest item–total correlations. For the SCOPA–AUT, one item was selected from each subdomain (constipation, urinary function, and cardiovascular function) based on the highest item–total correlation with the particular subdomain score. The SCOPA–COG is composed of four subdomains, but the 'visuo-spatial functions' subdomain consists of only one item; therefore, one item was selected from the subdomains 'memory and learning' (4 items), 'attention' (2 items), and 'executive functions' (3 items). All scales have answer options from 0 to 3, except the SCOPA–COG; SCOPA–COG scores were therefore first standardized to a maximum of 3, after which items were selected. These steps were repeated in the data of the fourth assessment of the PROPARK cohort and the ELEP cohort, to evaluate if the same items emerged in these datasets.

After selecting items for each domain, the Spearman's correlation coefficient between the sum score of the resulting 3 items and the original domain score was calculated in the baseline data of the PROPARK cohort to investigate if the 3-item score accurately approximated the original score. Cronbach's alpha was calculated for each 3-item domain score (recommended value $\geq$ 0.70) [17]. Subsequently, a principal component analysis (PCA) was conducted on the 6 domain scores to assess the interrelationships between the domains of the new scale. The Kaiser–Meyer–Olkin measure of sampling adequacy (KMO) was used to evaluate whether the sample size was adequate for factor analysis, where values $\geq$ 0.7 are considered as good [18]. Bartlett's test of sphericity evaluates whether the correlation matrix differs significantly from an identity matrix, a test that should be significant at $p < 0.05$ [18]. Internal consistency of the 18 selected items was evaluated with Cronbach's alpha, item homogeneity (mean of inter-item correlation coefficients; recommended value 0.15–0.50 [19]), and corrected item–total correlations (recommended value $\geq$ 0.30 [20]). The sum of the 18 items was correlated with the original 51-items PND-complex score to evaluate equivalence of the two scores (Spearman's correlation coefficient). Floor and ceiling effects were considered absent if $\leq$ 15% of patients attained the minimum or maximum scores [21]. Convergent validity was evaluated by calculating Spearman's correlation coefficient with the non-motor part of the MDS–UPDRS in the PROPARK2 study (N = 150; see for details Supplement 1). Correlations (Spearman's correlation) with H&Y, adjusted SPES/SCOPA motor score (PIGD items excluded), disease duration and age were also evaluated. Known-groups validity was assessed by comparing SENS-PD scores of patients in different H&Y stages using ANOVA. Data of patients who participated in year 1 and 4 of the PROPARK cohort were used to evaluate change in SENS-PD score over time, where the SENS-PD score in year 1 was subtracted from that in year 4.

To test for the assumption that the SENS-PD scale is relatively insensitive to dopaminergic medication, a linear regression analysis was conducted with the SENS-PD score as dependent variable and LDE as independent variable. Because disease severity and use of dopaminergic medication are related, the analysis was corrected for age, sex, disease duration, H&Y, and severity of dopaminergic symptoms (SPES/SCOPA motor score). Statistics were performed using SPSS 20.0 software.