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Segmental progression of cardinal motor symptoms in Parkinson's disease: A pilot study suggesting a practical approach to rate disease course in the early stages

Marina Picillo [a], Marianna Amboni [b], Roberto Erro [a], Carmine Vitale [b,c], Katia Longo [b], Maria Teresa Pellecchia [d], Autilia Cozzolino [d], Marcello Moccia [a], Roberto Allocca [a], Paolo Barone [d,*]

[a] Department of Neurological Sciences, University Federico II, Naples, Italy
[b] IDC Hermitage-Capodimonte, Naples, Italy
[c] University Parthenope, Naples, Italy
[d] Center for Neurodegenerative Diseases (CEMAND), Department of Medicine and Surgery, University of Salerno, Italy

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ABSTRACT

Little is known about the anatomical progression over the body segments of extrapyramidal signs in Parkinson's disease (PD); furthermore a great unmet need is the availability of instruments able to detect disease progression, even in the early phase.

The purpose of this study is to demonstrate that assessing topographical distribution of the cardinal motor features of PD may significantly improve the evaluation of disease progression in the early stages.

Forty-four drug-naïve PD patients were included in the study. Presence or absence of bradykinesia, rest tremor and rigidity was derived from Unified Parkinson's disease rating scale part III (UPDRS-III) in five different anatomical segments: axial, right and left upper- and lower-limbs. Based on this approach, four new scores were computed evaluating the anatomical spread of the cardinal motor symptoms of PD on the five body segments over a 18-month follow-up period. The four new scores included: the Bradykinesia Segmental Score, the Tremor Segmental Score, the Rigidity Segmental Score, measuring the occurrence of each motor symptom in different segments and the Combined Segmental Score evaluating the occurrence of any motor symptom in different anatomical regions. Data were analyzed using a repeated measures analysis of variance.

The Combined Segmental Score showed a significant progression over time whereas the Hoehn and Yahr and the UPDRS-III scores did not.

We suggest that a simple approach evaluating the anatomical distribution of motor symptoms and their progression over the body segments may be a useful complement to the classical rating tools to assess progression in early PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder for which only symptomatic treatments exist. When disease-modifying drugs are available, it will be crucial both to involve patients in the earliest phase of disease in clinical trials and to have instruments able to detect short-term progression of the disease.

Current rating tools, such as the Unified Parkinson's disease rating scale (UPDRS) [1] and the Hoehn and Yahr scale (H&Y) [2], are indeed poorly efficacious in detecting short-term progression of motor features, especially in the early stage of disease, when motor symptoms are mild [3]. In the ADAGIO study, the concept of slope analysis of UPDRS decline has been added as a novel measure of disease progression [4]. Recently, Schupbach and colleagues prospectively analyzed the anatomical progression of motor signs over a period of 12 months in twelve de novo, drug-naïve PD patients, using a sophisticated self-developed, semi-quantitative assessment battery which evaluates the severity of PD cardinal signs in all the major joints and muscle groups of the body [5]. Applying this approach, they suggested that a segmental examination of tremor and rigidity, combined with the bradykinesia scores from the UPDRS part III (UPDRS-III), is more sensitive than UPDRS-III alone in

* Corresponding author. Tel./fax: +39 089 672328.
E-mail address: pbarone@unisa.it (P. Barone).

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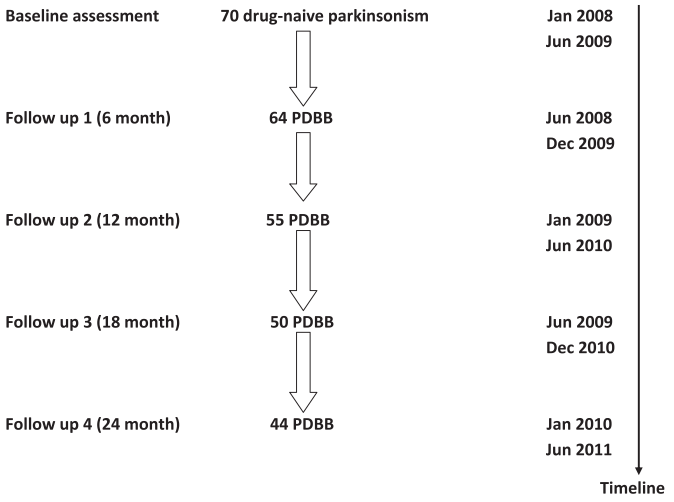

Fig. 1. Flow chart illustrating the timeline of the study. PDBB: PD according to the UK Parkinson's disease Society Brain Bank criteria. Only patients (44) with at least four assessments "on drug" were included in the analysis.

detecting changes in disease severity in early untreated PD patients over the course of one year [5]. Although it seems to be interesting and potentially useful, this approach is time-consuming and not easily applicable in clinical practice.

Our study has set out to evaluate the progression of motor symptoms in PD at very early stage of disease. Hence, we prospectively assessed the occurrence of bradykinesia, rest tremor and rigidity in five different anatomical segments, namely axial region, right and left upper limbs, right and left lower limbs over a period of 18 months. The evaluation used a new practical approach which scored the different motor symptoms by their occurrence over time in the different body parts.

2. Methods

2.1. Patients

Seventy de novo, drug-naïve patients with parkinsonism consecutively referred to the Department of Neurological Sciences of the University "Federico II" of Naples between January 1, 2008 and June 30, 2009 were approached to take part in the study. Inclusion criteria were: 1) the presence of parkinsonian syndrome according to United Kingdom Parkinson's Disease Society Brain Bank Diagnostic criteria (bradykinesia associated to tremor or rigidity or postural instability) [6]; 2) disease duration less than 2 years; 3) no history of present or past therapy with anti-parkinsonian agents. Exclusion criteria were: 1) diagnosis of secondary or atypical parkinsonism according to the available clinical criteria [7–10]; 2) known diagnosis of genetic parkinsonism (i.e. parkin, LRRK2, alfa-synuclein mutations-related parkinsonism); 3) lack of significant cerebral lesions at the MRI and/or CT, performed at baseline to exclude secondary parkinsonism (e.g. vascular parkinsonism, parkinsonism due to brain lesions); 4) present or past therapy with typical neuroleptics. Furthermore all patients were asked to perform a SPECT with ^{123}I-FP-CIT to confirm the dopaminergic dysfunction.

At the baseline evaluation the patients were drug-naïve; subsequently, due to the observational nature of the study, the patients were treated with anti-parkinsonian drugs according to physician's opinion. Then, they were evaluated "on drug" at 6, 12, 18 and 24 months and their medication dose was recorded as the levodopa equivalent dose (LED) [11]. Thus, progression of motor symptoms was evaluated based on changes on motor scores over an 18 month follow-up. In order to improve sensitivity of statistical analysis, we only included patients who underwent all four clinical assessments "on drug" (6, 12, 18 and 24 month assessments). The flowchart in Fig. 1 illustrates the case identification process. Patients not included in the analysis did not present significantly different demographic and/or clinical characteristics at baseline as compared to the cohort included in the analysis. The study was approved by the local ethics committee and written informed consent was obtained from all patients according to the Declaration of Helsinki.

2.2. Assessments and outcome measures

2.2.1. Classical rating scales

At each visit patients were examined with the UPDRS-III and the H&Y. In addition, a subscore for symptoms relatively refractory to dopaminergic medications was computed from UPDRS-III items, in agreement with Levy et al., [12] (i.e. UPDRS dopa-resistant score, encompassing scores for speech, posture, gait, postural stability and rising from sitting). Disability was evaluated using the Schwab and England Activities of Daily Living Scale (SE) [1] administered only at 6- and 24-month assessments. At the end of the follow-up period, our patients were

Table 1
Presence or absence of each motor symptom (bradykinesia, rest tremor and rigidity) was derived from UPDRS-III in five different anatomical segments: axial, right and left upper limbs, right and left lower limbs. Gait impairment was selected as an axial manifestation of bradykinesia. On this basis three new scores were computed and assessed at each visit: the Bradykinesia Segmental Score (BSS), the Tremor Segmental Score (TSS) and the Rigidity Segmental Score (RSS). These scores therefore range from 0 (symptom absent in all five segments) to 5 (symptom present in all five segments). Moreover, as a combination of the above-mentioned scores, we computed the Combined Segmental Score which evaluates the presence of any of the three motor symptoms in any anatomical region with a score ranging from 0 (no segment involved) to 5 (five segments involved).

Segments / Signs	Axial segment	Right Upper limb	Left Upper limb	Right Lower limb	Left Lower limb	
Bradykinesia	Gait (Item 29)	Finger Tapping (Item 23 - right arm subscore)	Finger Tapping (Item 23 - left arm subscore)	Leg Tapping (Item 26 - right leg subscore)	Leg Tapping (Item 26 - left leg subscore)	**Bradykinesia Segmental Score (range 0-5)**
Rest Tremor	Rest Tremor (Item 20 - head subscore)	Rest Tremor (Item 20 - right arm subscore)	Rest Tremor (Item 20 - left arm subscore)	Rest Tremor (Item 20 - right leg subscore)	Rest Tremor (Item 20 - left leg subscore)	**Tremor Segmental Score (range 0-5)**
Rigidity	Rigidity (Item 22 - axial subscore)	Rigidity (Item 22 - right arm subscore)	Rigidity (Item 22 - left arm subscore)	Rigidity (Item 22 - right leg subscore)	Rigidity (Item 22 - left leg subscore)	**Rigidity Segmental Score (range 0-5)**
Presence of any sign per segment	**0/1**	**0/1**	**0/1**	**0/1**	**0/1**	**Combined Segmental Score (range: 0-5)**

*items 20, 22, 23, 26, 29
UPDRS-III: Unified Parkinson's disease rating scale part III.