Parkinsonism and Related Disorders 40 (2017) 40–46

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Utility of the new Movement Disorder Society clinical diagnostic criteria for Parkinson's disease applied retrospectively in a large cohort study of recent onset cases

Naveed Malek, MD [a, *], Michael A. Lawton, MPhil [b], Katherine A. Grosset, MD [c], Nin Bajaj, PhD [d], Roger A. Barker, PhD [e], Yoav Ben-Shlomo, MD, PhD [b], David J. Burn, MD [f], Tom Foltynie, PhD [g], John Hardy, PhD [h], Huw R. Morris, PhD [i], Nigel M. Williams, PhD [j], Nicholas Wood, PhD [k], Donald G. Grosset, MD [c], on behalf of the PRoBaND clinical consortium

[a] Department of Neurology, Ipswich Hospital NHS Trust, Ipswich, United Kingdom
[b] School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom
[c] Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, United Kingdom
[d] Department of Neurology, Queen's Medical Centre, Nottingham, United Kingdom
[e] Department of Clinical Neurosciences, John van Geest Centre for Brain Repair, Cambridge, United Kingdom
[f] Institute of Neuroscience, University of Newcastle, Newcastle upon Tyne, United Kingdom
[g] Sobell Department of Motor Neuroscience, UCL Institute of Neurology, London, United Kingdom
[h] Reta Lila Weston Laboratories, Department of Molecular Neuroscience, UCL Institute of Neurology, London, United Kingdom
[i] Department of Clinical Neuroscience, UCL Institute of Neurology, London, United Kingdom
[j] Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, United Kingdom
[k] Department of Molecular Neuroscience, UCL Institute of Neurology, London, United Kingdom

ARTICLE INFO

Article history:
Received 30 January 2017
Received in revised form
8 April 2017
Accepted 10 April 2017

Keywords:
Parkinson's disease
Diagnosis
Phenotype
Criteria

ABSTRACT

Objective: To examine the utility of the new Movement Disorder Society (MDS) diagnostic criteria in a large cohort of Parkinson's disease (PD) patients.
Methods: Recently diagnosed (<3.5 years) PD cases fulfilling United Kingdom (UK) brain bank criteria in *Tracking Parkinson's*, a UK multicenter prospective natural history study were assessed by retrospective application of the MDS criteria.
Results: In 2000 cases, 1835 (91.7%) met MDS criteria for PD, either clinically established (n = 1261, 63.1%) or clinically probable (n = 574, 28.7%), leaving 165 (8.3%) not fulfilling criteria. Clinically established cases were significantly more likely to have limb rest tremor (89.3%), a good L-dopa response (79.5%), and olfactory loss (71.1%), than clinically probable cases (60.6%, 44.4%, and 34.5% respectively), but differences between probable PD and 'not PD' cases were less evident. In cases not fulfilling criteria, the mean MDS UPDRS3 score (25.1, SD 13.2) was significantly higher than in probable PD (22.3, SD 12.7, $p = 0.016$) but not established PD (22.9, SD 12.0, $p = 0.066$). The L-dopa equivalent daily dose of 341 mg (SD 261) in non-PD cases was significantly higher than in probable PD (250 mg, SD 214, $p < 0.001$) and established PD (308 mg, SD 199, $p = 0.025$). After 30 months' follow-up, 89.5% of clinically established cases at baseline remained as PD (established/probable), and 86.9% of those categorized as clinically probable at baseline remained as PD (established/probable). Cases not fulfilling PD criteria had more severe parkinsonism, in particular relating to postural instability, gait problems, and cognitive impairment.

* Corresponding author. Department of Neurology, Ipswich Hospital NHS Trust, Ipswich IP4 5PD, United Kingdom.
E-mail address: nmalek@nhs.net (N. Malek).

http://dx.doi.org/10.1016/j.parkreldis.2017.04.006
1353-8020/

Conclusion: Over 90% of cases clinically diagnosed as early PD fulfilled the MDS criteria for PD. Those not fulfilling criteria may have an atypical parkinsonian disorder or secondary parkinsonism that is not correctly identified by the UK Brain Bank criteria, but possibly by the new criteria.

1. Introduction

The accurate diagnosis of Parkinson's disease (PD) assists patient management and healthcare planning, and the identification of effective new treatments, which is important for a disease with an increasing prevalence [1]. Clinical diagnostic accuracy is suboptimal, being around 80% based on an overview of 11 studies [2] [3]. As there is no biomarker or specific imaging test for PD, the diagnosis relies heavily on clinical assessment [4]. Increased knowledge about PD and disorders that mimic it has allowed the development of new clinical Movement Disorder Society (MDS) diagnostic criteria [4]. These retain the core definition of parkinsonism (bradykinesia, rigidity and/or rest tremor) but do not allow for postural instability, compared to the United Kingdom (UK) Brain Bank criteria [5]. After confirmation of parkinsonism, a clinical diagnosis of PD according to the MDS criteria is based on: absolute exclusion criteria (which rule out PD), red flags (which must be counterbalanced by supportive criteria), and positive supportive criteria. These are combined to determine diagnostic certainty as clinically probable PD, or clinically established PD [4]. The new consensus criteria represent a summation of available knowledge, but have not been tested prospectively, which was the purpose of the current study. We classified and described the phenotype of cases recruited to an observational study of PD, according to fulfilment of the new MDS criteria [4].

2. Methods

Patients were recruited to *Tracking Parkinson's*, a large prospective, UK multicenter project, as detailed elsewhere [6]. In brief, recent onset PD cases with a clinical diagnosis and fulfilling UK Brain Bank criteria at study entry [5] were recruited, including drug-naïve and treated patients. Those with severe comorbid illness, other degenerative parkinsonism, symmetrical lower body parkinsonism, drug-induced parkinsonism, or a clinical diagnosis of dementia at first assessment were excluded. Levodopa (L-dopa) equivalent daily doses (LEDD) were calculated using an established formula [7]. Motor subtypes were determined by established methods [8]. Montreal cognitive assessment (MoCA) scores were adjusted for years of education and categorized as normal (>23), mild cognitive impairment (MCI) (22–23, or less than 22 but without functional impairment), or dementia (21 or less with functional impairment) [9]. Olfaction testing used either the 40-item University of Pennsylvania Smell Identification Test (UPSIT) or Sniffin' Sticks 16-item version (SS), and hyposmia was defined as previously reported [10]. FP-CIT scanning was performed as part of routine care, on the basis of diagnostic uncertainty.

As the MDS diagnostic criteria were published after patient recruitment was complete, the criteria were applied retrospectively. Each component was mapped to the assessments performed, including MDS UPDRS, lying and standing blood pressure, response to L-dopa test dose, non-motor symptom scales, scales for outcome in autonomic symptoms in PD, PD and Epworth sleep score, and questionnaires for wearing off, rapid eye movement behavior disorder, constipation, Leeds anxiety and depression, and PD quality of life. Clinicians assessed each case, at baseline (study entry) and after 1 and 2.5 years, for any unusual or atypical features for PD, under several categories: clinical presentation, symptoms, signs, disease course, or therapy response. To ensure that early signs were not overlooked, such features were noted when they 'could indicate an alternative diagnosis to PD (i.e. idiopathic parkinsonism with the presence of Lewy bodies in the substantia nigra), no matter how remote'. Clinicians also rated their clinical diagnostic certainty between 0% (not PD) and 100% (definite PD).

There was some variance in the data elements collected, compared to the MDS criteria: we recorded vertical gaze palsy (rather than only downward vertical gaze palsy), and did not specifically note recurrent falls, inspiratory stridor, or frequent inspiratory sighs. We assessed for the absence of an observable L-dopa response following MDS criteria (daily L-dopa dose 600 mg or more, and bradykinesia or rigidity in at least one body part exceeding 2 points), and carried out an additional exploratory analysis (no L-dopa dose threshold, MDS UPDRS 3 score above 20 to define at least moderate disease, and clinician assessment of 'little or no response to L-dopa or a dopamine agonist'). For assessment of a clear and dramatic response to dopaminergic therapy, we used an improvement of over 30% in MDS UPDRS 3 after the patient's usual morning L-dopa dose, taken after a practically defined overnight period off medication.

2.1. Statistical analysis

Regression models were used to test the association between the three MDS classification groups and clinical features. Clinical characteristics were the dependent variables and the MDS criteria groups (along with age, gender and disease duration) were the independent variables. Regression was linear for continuous outcomes, logistic for binary outcomes, ordinal (also called proportional odds) for ordinal outcomes (MoCA and Hoehn and Yahr stage), and multinomial for motor subtype (using tremor dominant as the baseline category). Two-way p-values across the three MDS classification groups were calculated as 2-tailed, after adjustment for three confounders: age, gender and disease duration. The linearity of age and disease duration was tested using fractional polynomials in univariate models, and then transformed if nonlinear. The results were not corrected for multiple comparisons. The agreement between baseline and follow-up categorization was tested using weighted kappa, and also, because of imbalance of group sizes and numbers of cases changing category, by the weighted Gwet AC1/AC2 coefficient [11,12]. Statistical analysis was conducted using STATA (version 14, StataCorp, Texas, USA).

3. Results

There were 2000 cases at study entry, mean age 64.4 years (SD 9.8), disease duration 1.3 years (SD 0.9), and 64.9% were male. 1835 (91.7%) met the MDS diagnostic criteria for PD, either clinically established (n = 1261, 63.1% of all cases) or clinically probable (n = 574, 28.7% of all cases), leaving 165 (8.3% of all cases) who did not meet criteria (Table 1). Tremor as a symptom at onset was significantly more prevalent in clinically established PD (83.3%) than clinically probable PD (57.4%), or those not fulfilling criteria for