Movement Disorder Society Criteria for Clinically Established Early Parkinson's Disease

Daniela Berg, MD,[1,2]* Charles H. Adler, MD, PhD,[3] (iD)
Bastiaan R. Bloem, MD, PhD,[4] Piu Chan, MD, PhD,[5]
Thomas Gasser, MD,[2] Christopher G. Goetz, MD,[6]
Glenda Halliday, PhD,[7] (iD) Anthony E. Lang, OC, MD, FRCPC
,[8] (iD) Simon Lewis, MD,[9] Yuan Li, MD, PhD,[5]
Inga Liepelt-Scarfone, PhD,[2,10] Irene Litvan, MD,[11]
Kenneth Marek, MD,[12] Corina Maetzler,[1]
Taomian Mi, MD, PhD,[5] José Obeso, MD, PhD,[13]
Wolfgang Oertel, MD,[14] C. Warren Olanow, MD, FRCPC,[15]
Werner Poewe, MD,[16] Silvia Rios-Romenets, MD,[17]
Eva Schäffer, MD,[1] Klaus Seppi, MD,[16] Beatrice Heim, MD,[16]
Elizabeth Slow, MD, FRCPC,[8] Matthew Stern, MD,[18]
Ian O. Bledsoe,[19] Günther Deuschl, MD[1] (iD) and
Ronald B. Postuma, MD, MSc[17]*

[1]Department of Neurology, Christian-Albrechts-University of Kiel, Kiel, Germany [2]Department of Neurodegeneration, Hertie-Institute for Clinical Brain Research, Tübingen, Germany [3]The Parkinson's Disease and Movement Disorders Center, Department of Neurology, Mayo Clinic, Scottsdale, Arizona, USA [4]Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Netherlands [5]Xuanwu Hospital of Capitol of Medical University, Beijing, Peoples Republic of China [6]Rush University Medical Center, Chicago, Illinois, USA [7]Neuroscience Research Australia & University of New South Wales, Randwick, Australia [8]Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, Ontario, Canada [9]Brain and Mind Centre University of Sydney, Camperdown, Australia [10]German Center for Neurodegenerative Diseases, Tübingen, Germany [11]Department of Neurosciences, University of California San Diego, La Jolla, California, USA [12]Institute for Neurodegenerative Disorders, New Haven, Connecticut, USA [13]University of Navarra-Fundación para la Investigación Médica Aplicada (FIMA), Pamplona, Spain [14]Department of Neurology, Philipps University of Marburg, Marburg, Germany [15]Department of Neurology, Mount Sinai School of Medicine, New York, New York, USA [16]Department of Neurology, Innsbruck Medical University, Innsbruck, Austria [17]Department of Neurology, Montreal General Hospital, Montreal, Quebec, Canada [18]Penn Neurological Institute, Philadelphia, Pennsylvania, USA [19]University of California, San Francisco, California, USA

---

*Corresponding authors: Dr. Ronald B. Postuma, Department of Neurology, L7-305 Montreal General Hospital, 1650 Cedar Ave, Montreal, Canada H3G1A4; ron.postuma@mcgill.ca; Dr. Daniela Berg, Department of Neurology, Christian-Albrechts-University of Kiel, Arnold-Heller-Str. 3 24105 Kiel; Daniela.berg@uksh.de

ABSTRACT: Background: In 2015, the International Parkinson and Movement Disorder Society published clinical diagnostic criteria for Parkinson's disease (PD). Although recent validation studies suggest high accuracy, one unmet need is for highly specific criteria for clinical trials in early/de novo PD.
Objectives: The objective of this study was to generate and test a PD diagnostic criteria termed "clinically established early PD."
Methods: We modified the Movement Disorder Society criteria to increase specificity for early PD by removing all disease duration components and changing red flags to absolute exclusions. We then estimated the sensitivity/specificity of clinically established early PD criteria in patients with disease duration <5 years, selected from a 626-patient validation study.
Results: After documentation of parkinsonism, 18 individual exclusion criteria are assessed that preclude the diagnosis of "clinically established early PD." Among 212 PD and 152 non-PD patients, the estimated specificity was 95.4%, with 69.8% sensitivity.
Conclusions: We describe high-specificity criteria for de novo PD, which are freely available for use in clinical trials. © 2018 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; diagnosis; criteria

In 2015, a task force of the International Parkinson and Movement Disorder Society (MDS) published new clinical diagnostic criteria for Parkinson's disease.[1–3] These included criteria for both prodromal PD[3] and clinical PD.[2] A clinical PD diagnosis was divided into the following 2 levels of certainty: probable PD (aimed to have both 80% sensitivity and specificity) and clinically established PD (aimed to optimize specificity without regard to sensitivity). Validation of these criteria was recently completed (see Postuma and colleagues[4]) and demonstrated 94.5% sensitivity and 88.5% specificity for probable PD.

As putative neuroprotective therapies are being evaluated in de novo PD, it is essential to find criteria that can identify early PD with high specificity to minimize variability associated with error in diagnosis. In general, the clinical diagnosis of PD becomes easier as disease duration increases[5–7]; diagnosing de novo untreated PD is particularly difficult because the response to dopaminergic therapy remains undefined.

To address this need, we generated new clinical diagnostic criteria for early PD, termed "Clinically Established Early PD." These criteria were designed to provide a high specificity for diagnosis of untreated/early PD patients, especially for use in therapeutic trials that require high specificity, but could accept a sensitivity lower than the 80% benchmark for probable PD. Results from the criteria validation study were used to estimate sensitivity and specificity of the new criteria.

Methods

To design the "Clinically Established Early PD" criterion, we revised each individual criterion from the original MDS criteria[2] to allow application in early and untreated PD, as follows:

1. All duration components from the original criteria (eg, falls within the first 3 years, absent nonmotor PD despite 5 years duration, etc.) were removed.
2. Criteria that can only be applied with long-duration disease were removed (eg, absence of progression over 5 years).
3. All red flags were now defined as absolute exclusion criteria (this optimizes specificity and also allows a simple exclusion criteria checklist for clinical trials). This implies that supportive criteria are no longer required to counterbalance a red flag, so supportive criteria are not included in the early-PD category. Note also that 2 of the supportive criteria required levodopa treatment (ie, dramatic levodopa response and dyskinesia) and thus do not apply to de novo PD and that hyposmia remains in the criteria as 1 of the markers that can document nonmotor parkinsonism (see criterion 15, Fig. 1).

Methods for the validation have been described elsewhere.[4] Briefly, we tested the sensitivity and specificity of the MDS criteria in 626 patients with parkinsonism from 8 centers. The diagnosis of PD (n = 434) versus not PD (n = 192) was made according to the clinical gold standard by an experienced task force neurologist using all relevant clinical information available during the entire disease course, including any ancillary tests that were available (without using MDS criteria). Then, a second neurologist assessed only the presence or absence of each individual criterion from the MDS criteria. Each center's local research ethics board approved the study protocol and informed written consent was obtained from all patients.

We performed estimates of diagnostic utility based on data from the validation study. The primary outcome was the accuracy/concordance of MDS clinically established early PD criteria against the gold-standard clinical diagnosis in patients with disease duration <5 years. Note that the accuracy assessments are an estimate only because there are subtle differences in the wordings and definitions of the criteria of the original MDS criteria and the clinically established early criteria and validation was performed with the original MDS criteria wording.

Results

The MDS clinically established early PD criteria are presented in Figure 1. As in previous MDS criteria, the documentation of parkinsonism (bradykinesia with at least 1 of rigidity or rest tremor) is required. Then the criteria are used to identify markers that argue against PD as the cause of parkinsonism. For the new category of clinically established early PD, there are 18 exclusion criteria, each based on the original MDS criteria. The details on how each criterion should be assessed and rated are provided in the original MDS criteria article.[2] Documentation of any 1 of these markers rules out a diagnosis of clinically established early PD (note that MDS probable PD can still be diagnosed in patients who do not meet the clinically established criteria).

To estimate the sensitivity and specificity of the criteria, we selected 366 patients with disease duration <5 years from the validation study (Table 1). Of the patients, 212 had PD and 152 had non-PD parkinsonism according to clinical gold-standard diagnosis. Of the non-PD group, the most common conditions were multiple system atrophy (38%), progressive supranuclear palsy (30%), corticobasal syndrome (12%), and vascular parkinsonism (6%).

Of the non-PD patients, 95.4% were correctly identified as non-PD by the clinically established early criteria (ie, specificity = 95.4%, false positive rate = 4.6%), and 68.9% of PD patients met these criteria (Table 1).

Compared to the overall criteria for PD published in 2015, 46.7% of the PD patients with <5 years duration met criteria for the overall 2015 MDS clinically established PD category (and 1.3% of non-PD patients met the 2015 clinically established PD criteria). This implies that the current adaptation of the criteria for short-duration PD increased sensitivity by 22.2% at a specificity cost of 3.3%. By contrast, we obtained a sensitivity/specificity of probable PD of 92.8/86.8 in this <5-year duration group (the criteria were originally designed to obtain at least 80% sensitivity and specificity). So, when compared to probable PD, the use of the clinically established early PD criteria reduced sensitivity by 23.9%, but increased specificity by 8.6%, translating to a 65% relative reduction of the false positive rate (ie, from 13.2% to 4.6%). If analysis was restricted to patients with ≤1 year duration, accuracy was only slightly lower (sensitivity = 64.3%, specificity = 94.5%).

These criteria are designed specifically for studies of early PD (duration < 5 years) in which specificity needs to be optimized. The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the International Parkinson and Movement Disorders Society–Unified Parkinson Disease Rating Scale. Once parkinsonism has been diagnosed, documentation of any of these features rules out the diagnosis of clinically established early PD.

☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia or cerebellar oculomotor abnormalities (e.g. sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades).

☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades

☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia.

☐ 4. Parkinsonian features restricted to the lower limbs.

☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism

☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease

☐ 7. Unequivocal cortical sensory loss (i.e. graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia

☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system.

☐ 9. Gait impairment requiring regular use of wheelchair.

☐ 10. **Severe** dysphonia/dysarthria (speech unintelligible most of the time) and/or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding).

☐ 11. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor and/or frequent inspiratory sighs.

☐ 12. Severe Autonomic Dysfunction: either a) Orthostatic hypotension - orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
      b) Severe urinary retention or urinary incontinence (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be due to prostate disease, and must be associated with erectile dysfunction.

☐ 13. Recurrent (>1/year) falls due to impaired balance.

☐ 14. Disproportionate anterocollis (dystonic) and/or contractures of hand or feet.

☐ 15. Absence of any of the common non-motor features of disease. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations).

☐ 16. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness and/or clear pathologic hyper-reflexia (excluding mild reflex asymmetry and isolated extensor plantar response).

☐ 17. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination.

☐ 18. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based upon the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD.

FIG. 1. Criteria for Clinically Established Early Parkinson's Disease.

Discussion

Recognizing the need for high-specificity diagnosis in early (and often untreated) PD patients, we present here the MDS clinically established early PD criteria. These criteria are an adaptation of the original MDS criteria, retaining the core definition of parkinsonism, but modified by treating any red flags as absolute exclusions and removing the supportive criteria and disease duration components. Based on the validation database, this appears to provide excellent specificity (95.4%) with sufficient sensitivity (68.9%) so as to permit accurate and efficient recruitment for clinical trials.

These criteria were designed especially for use in clinical trials of early PD. Increasing evidence suggests that it is necessary to conduct clinical trials of putative

TABLE 1. Study population and MDS criteria accuracy

	PD, n = 212	Non-PD parkinsonism, n = 152
Age	65.3 ± 11.2	67.6 ± 10.0
Sex (% female)	32.1	40.1
Disease duration from diagnosis (y)	1.9 ± 1.4	1.8 ± 1.4
Meets MDS clinically established early PD (%)	68.9	4.6
Meets MDS probable criteria (%)	92.8	13.2
Meets MDS clinically established (%)	46.7	1.3

Note that because the wording of individual criteria differs in the new Clinically Established Early PD Criteria, the diagnostic accuracy provided for this category should be considered as an estimate. MDS, International Parkinson and Movement Disorders Society.

neuroprotective therapies in early PD patients, when there is sufficient preservation of dopamine neurons to permit a beneficial effect. Diagnosis of early PD can be difficult; atypical markers may not have had the time to emerge, and the essential diagnostic hallmark of a good levodopa response may not have been tested. Diagnostic inaccuracy represents a major barrier to conducting disease-modifying trials in newly diagnosed patients with PD. Although low diagnostic sensitivity can be somewhat problematic for clinical trials in PD patients (as a result of poor recruitment and potential impacts on generalizability), the loss of diagnostic accuracy can be detrimental to studies in early PD. For example, one may assume an agent that reduces the progression of MDS-UPDRS by 4 ± 8 points when compared with the placebo group. Using a basic t-test (assuming equal standard deviations), a sample size of 126 patients would be needed for 80% power to find a difference. If, however, 25% of the population is misclassified and does not have PD (and so has no therapeutic response), the observed difference drops to 3 ± 8 points, and the sample size must be nearly doubled to 225 patients. With an estimated specificity of 95% compared to the clinical gold standard, our new criteria allow the use of a specific standardized diagnostic procedure for entry into clinical trials of early PD.

Despite the specificity advantage, these criteria are not meant to replace the MDS probable PD category for all studies of early PD. Using these highly specific criteria will have important trade-offs for generalizability. For example, patients with diffuse malignant forms of PD[8] will be excluded because of factors such as early autonomic dysfunction or balance problems. Moreover, patients with pure-motor subtypes may be excluded because of factors such as absent nonmotor features. The MDS probable PD criteria better reflect the diagnostic process of clinicians, and for any study in which representativeness is important, the probable PD category should be prioritized.

Some limitations of this study should be noted. First, it must be emphasized that the gold standard from the validation study was a clinical gold-standard diagnosis, which will obviously be wrong in some cases, especially in the early stage of PD.[5–7,9,10] Therefore, the estimates of sensitivity and specificity are different than one might obtain with prolonged clinical follow-up and particularly with pathologic validation. Second, the estimates of diagnostic utility from this study were made from the individual 2015 criteria that for some items have slight differences in wording and/or structure from the current clinically established early PD criteria (eg, disease duration components are removed in the current version). These differences would result in somewhat different sensitivity/specificity estimates. Third, the diagnostic utility estimates include all patients with <5 years duration, and if the criteria are used specifically in only untreated PD, sensitivity/specificity may differ. Note, however, the role of very short disease duration in determining accuracy was modest in this validation study; accuracy for disease duration <1 year was approximately equal to the entire study population.

In summary, the MDS task force proposes here the first highly specific diagnostic criteria designed for targeted intervention trials in patients with early PD. We offer the criteria to be freely used and without restrictions for clinical practice, clinical trial protocols, and trial documentation. ●

References

1. Berg D, Postuma RB, Bloem B, et al. Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. Mov Disord 2014;29:454-462.

2. Postuma RB, Berg D, Stern M, et al. MDS Clinical Diagnostic Criteria for Parkinson's disease. Mov Disord 2015;30:1591-1600.

3. Berg D, Postuma RB, Adler CH, et al. MDS Research Criteria for Prodromal Parkinson's Disease. Mov Disord 2015;30:1600-1611.

4. Postuma RB, Poewe W, Litvan I, et al. Validation of the MDS Clinical Diagnostic Criteria for Parkinson's Disease [published online ahead of print 2018]. Mov Disord. In press.

5. Respondek G, Kurz C, Arzberger T, et al. Which ante mortem clinical features predict progressive supranuclear palsy pathology? Mov Disord 2017;32:995-1005.

6. Adler CH, Beach TG, Hentz JG, et al. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. Neurology 2014;83:406-412.

7. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002;125:861-870.

8. Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. Brain 2017;140:1959-1976.

9. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-184.

10. Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism--a prospective study. Can J Neurol Sci 1991;18:275-278.