REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

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ABSTRACT: This document presents the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease (PD). The Movement Disorder Society PD Criteria are intended for use in clinical research but also may be used to guide clinical diagnosis. The benchmark for these criteria is expert clinical diagnosis; the criteria aim to systematize the diagnostic process, to make it reproducible across centers and applicable by clinicians with less expertise in PD diagnosis. Although motor abnormalities remain central, increasing recognition has been given to nonmotor manifestations; these are incorporated into both the current criteria and particularly into separate criteria for prodromal PD. Similar to previous criteria, the Movement Disorder Society PD Criteria retain motor parkinsonism as the core feature of the disease, defined as bradykinesia plus rest tremor or rigidity. Explicit instructions for defining these cardinal features are included. After documentation of parkinsonism, determination of PD as the cause of parkinsonism relies on three categories of diagnostic features: absolute exclusion criteria (which rule out PD), red flags (which must be counterbalanced by additional supportive criteria to allow diagnosis of PD), and supportive criteria (positive features that increase confidence of the PD diagnosis). Two levels of certainty are delineated: clinically established PD (maximizing specificity at the

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expense of reduced sensitivity) and probable PD (which balances sensitivity and specificity). The Movement Disorder Society criteria retain elements proven valuable in previous criteria and omit aspects that are no longer justified, thereby encapsulating diagnosis according to current knowledge. As understanding of PD expands, the Movement Disorder Society criteria will need continuous revision to accommodate these advances.

Key Words: Parkinson's disease; clinical diagnostic criteria; motor parkinsonism; non-motor manifestations; absolute exclusion criteria; red flags; supportive criteria

In this document, we propose criteria intended to be used as the official International Parkinson and Movement Disorder Society (MDS) Clinical Diagnostic Criteria for Parkinson's disease (MDS-PD Criteria). The criteria were designed specifically for use in research, but they also can be used as a general guide to clinical diagnosis of PD consequent to Lewy body pathology.

Methodology of Criteria Generation

The criteria emerged from the work of the MDS task force for the definition of PD; an introductory statement from the task force was recently published, as have criteria for prodromal PD.[1,2]

After completion of the definition statement,[1] the task force moved toward generation of diagnostic criteria. We held two open "brainstorming" teleconferences and an in-person meeting, from which the two primary authors created draft criteria. Once these were generated, each task force member checked this against their experience, offered comments, and so forth in a constant revision process that took place over the next 6 months.

After the final draft was completed, a phase of "cognitive pretesting" ensued, in which neurologists who were not familiar with the development of the criteria were asked to read, comment on, and then use the criteria in actual patients. This produced a further revised document, which is the manuscript. The criteria were finalized and ratified in San Diego, California, USA, in June 2015. A study testing their validity against gold standard clinical diagnosis is ongoing.

Several diagnostic criteria for PD were previously created and are variably used in the PD community.[3-6] The task force considered many elements of previously published criteria, and they served as a basis for the MDS-PD criteria. The UK brain bank criteria are the most commonly used criteria for PD at present; many elements of these criteria were used in the generation of the current criteria. Since publication of previous criteria, knowledge has advanced, and concepts of the disease are shifting[7]; therefore, whereas some features of previous criteria were retained, others were omitted or revised. Similarly, the task force is well aware that these criteria will also be revised as scientific advances allow better understanding of symptoms and disease course.

Several key aspects of the MDS-PD criteria deserve further emphasis, including the following:

Centrality of Motor Syndrome—Parkinsonism and PD

Since its original description, the clinical diagnosis of PD has centered on a defined motor syndrome. In the MDS-PD criteria, the centrality of the motor syndrome remains the core feature by which clinical PD is defined. However, nonmotor manifestations are present in most patients and often can dominate the clinical presentation. Many of these nonmotor manifestations have now been incorporated into the diagnostic criteria. Moreover, the pathological process of PD often begins in nondopaminergic structures of the brain or peripheral nervous system, during which nonmotor features often dominate. This is reflected in a new diagnostic classification, prodromal PD, which is considered to be a true stage of PD (ie, prodromal PD *is* PD). Prodromal PD has been defined in a parallel publication.[2]

Like previous criteria, the MDS criteria use a two-step process of PD diagnosis. First, parkinsonism is defined (as bradykinesia in combination with either rest tremor, rigidity, or both). Once diagnosed, the criteria then define whether this parkinsonism is attributable to PD.

Criteria Benchmark—The Expert Examination

Full diagnostic certainty is impossible during life; between 75% and 95% of patients diagnosed with PD by experts have their diagnosis confirmed on autopsy.[8-12] Diagnostic accuracy varies considerably according to disease duration (lower on first visit than after longer follow-up[13]), age, the expertise of the clinician, and evolution in our understanding of PD (more recent studies generally show higher accuracy). Diagnostic error can be attributable to failure to recognize other pathologies causing neurodegenerative or secondary parkinsonism (multiple system atrophy, progressive supranuclear palsy, subcortical arteriosclerotic encephalopathy, and so forth), or to the absence of a true progressive

parkinsonian disorder (essential tremor, dystonic tremor, and so forth). The MDS-PD Criteria are designed to minimize both of these diagnostic errors.

Of note, studies have suggested that experienced clinicians can diagnose PD with greater accuracy than formal diagnostic criteria.[9] Therefore, until definitive validated diagnostic markers are available, clinical expert opinion will be the gold standard diagnostic technique in life. Accordingly, the current criteria were designed to mimic and codify the diagnostic process of expert clinicians. Their goal is to improve reproducibility between raters and between centers in clinical research, and (with appropriate training) aid diagnosis by clinicians with less expertise in PD.

Certainty Levels

In creating diagnostic criteria, an inherent conflict exists between sensitivity and specificity. The relative importance of false negatives versus false positives varies according to the purpose for which criteria are applied. To account for multiple uses, the MDS-PD Criteria include two distinct levels of diagnostic certainty. These are:

1. Clinically Established PD: Maximizing specificity, the category is anchored with the goal that the large majority (ie, at least 90%) will have PD. It is presumed that many true PD cases will not meet this certainty level.
2. Clinically Probable PD: Balancing sensitivity and specificity, the category is anchored with the goal that at least 80% of patients diagnosed as probable PD truly have PD, but also that 80% of true PD cases are identified.

Other Key Features of the Criteria

As discussed in our introductory statement,[1] we incorporated numerous key features in the criteria. These include:

1. Negative and positive features: The criteria include "negative" features (absolute exclusions, red flags) that argue against a diagnosis of PD, and "positive" features (supportive criteria) that argue for PD diagnosis.
2. Weighting: Not all features are of equal importance in diagnosis. Therefore, negative diagnostic features were divided into absolute exclusion features, which are highly specific signs of alternate diagnoses incompatible with any diagnostic level of PD, and red flags, which are potential signs of alternate pathology with lower or uncertain specificity. Red flags rule out probable PD diagnosis only when they cannot be counterbalanced by supportive criteria. A benchmark for an absolute exclusion was occurrence in less than 3% of true PD, whereas specificity for red flags was not specifically defined. In some cases, specificity evidence was available,[14,15] but in others, evidence was less clear; for these, group consensus and previous guidance from prior criteria were used.
3. Interpretation of features: Some exclusion criteria include interpretative suggestions, so that they are not applied to situations that are inappropriate (for example, parkinsonism in a patient taking low-dose Quetiapine prescribed for sleep may not truly constitute "drug-induced parkinsonism"). In addition, because not all extenuating circumstances can be anticipated a priori, clinicians may "override" a specific criterion, provided that a confounding condition is clearly identified that unequivocally explains the criterion's presence (eg, cortical sensory loss after a stroke, "rapid progression" to wheelchair-bound state because of orthopedic injury, and so forth).
4. Time: Diagnostic accuracy generally increases with time; early in the disease course, progression and treatment response may be undefined, and hallmarks of other neurodegenerative diseases may not have yet emerged. Also, certain features have different implications in different disease durations; some "atypical" features are incompatible with early PD but may be relatively common in advanced PD. Therefore many individual criteria include duration components. If an atypical feature occurs outside the time window, the criterion is not applied (also, if the atypical feature is absent and disease duration still less than the time window, the criterion is not applied).
5. Dementia: As outlined in our introductory manuscript, the MDS-PD criteria do not consider dementia as an exclusion criterion for PD, regardless of when it occurs in relation to parkinsonism onset. For those patients with dementia who already carry a diagnosis of dementia with Lewy bodies (according to consensus criteria[16]), the diagnosis can optionally be qualified as "PD (dementia with Lewy bodies subtype)."
6. Ancillary Diagnostic Testing: Currently, PD diagnoses are generally made clinically, and the MDS criteria were designed to be broadly applicable without need for ancillary diagnostic testing. However, in certain contexts, ancillary testing is performed to resolve uncertain cases. Moreover, as knowledge advances, diagnostic biochemical markers, anatomical neuroimaging, and methods to detect alpha-synuclein deposition may become available.

   The MDS-PD criteria allow results from a reliable ancillary test to serve as a single supportive criterion. Such a marker must have been assessed as 80% or more specific in the differential diagnosis of parkinsonism (compared with gold-standard clinical or clinicopathologic diagnosis) in most studies. At minimum, three separate studies from different centers with at

least 60 participants (including ≥30 patients with non-PD parkinsonism) must have documented 80% or more specificity. A published meta-analysis combining studies with smaller numbers of patients could substitute for one qualifying study (two other studies with >30 patients in each group are still required). Currently, olfactory loss[17-25] and metaiodobenzylguanidine scintigraphy[26-29] meet this threshold, but others may eventually qualify. Note that although dopaminergic neuroimaging can help distinguish parkinsonism (ie, degeneration of the nigrostriatal system) from PD-mimics without parkinsonism (eg, essential tremor), it does not qualify as a criterion for the differentiation of PD from other parkinsonian conditions like atypical parkinsonian syndromes.

Following are the full MDS-PD criteria. An executive summary, which can be printed for use in clinical trial documentation, is provided in Table 1.

MDS Criteria—Full Version

I. Criteria for Parkinsonism

The prerequisite to apply the MDS-PD criteria is the diagnosis of parkinsonism, which is based on three cardinal motor manifestations. Parkinsonism is defined as bradykinesia, in combination with either rest tremor, rigidity, or both. These features must be clearly demonstrable and not attributable to confounding factors.

Note: Several large-scale studies document mild parkinsonian syndromes in up to 25% of elderly persons without PD. This mild nonspecific parkinsonism may be unrelated to synuclein deposition. The parkinsonism criteria aim to differentiate parkinsonism caused by clinical PD from these common mild parkinsonian syndromes, and also to create a threshold for identifying when a patient has evolved from prodromal PD to full clinical PD. Note also that although the MDS-Unified Parkinson's Disease Rating Scale (UPDRS) rates PD, it does not define it (eg, MDS-UPDRS bradykinesia scores do not specifically delineate a combination of slowness and decrement). Therefore, no single cutoff score on the MDS-UPDRS items should be used to define parkinsonism.

The "confounding factors" caveat does not imply that a parkinsonism diagnosis cannot be made if potential confounding factors exist (eg, arthritis, weakness); rather, examiner judgment should be used to decide whether examination findings are entirely attributable to confounding features, or whether additional parkinsonism is present.

Definition of Cardinal Parkinsonism Manifestations

Examination of all cardinal manifestations should be carried out as described in the Motor Examination section (Part 3) of the MDS-UPDRS (2008 version).[30]

Bradykinesia

Bradykinesia is defined as slowness of movement AND decrement in amplitude or speed (or progressive hesitations/halts) as movements are continued. Bradykinesia can be evaluated by using finger tapping (MDS-UPDRS 3.4), hand movements (3.5), pronation-supination movements (3.6), toe tapping (3.7), and foot tapping (3.8). Although bradykinesia also occurs in voice, face, and axial/gait domains, limb bradykinesia must be documented to establish a diagnosis of PD.

Note: Bradykinesia as defined here combines with one term the definitions of bradykinesia (slowness) and akinesia/hypokinesia (decreased movement amplitude); both are generally present on examination, although not always simultaneously (ie, patients cannot move at normal speed with normal amplitude). In parkinsonism caused by PD, a decline in either speed or amplitude is seen as movements are continued, a feature sometimes not observed in parkinsonism caused by alternate conditions.

Rigidity

As outlined in the MDS-UPDRS, rigidity is judged on "slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck." Rigidity refers to "lead-pipe" resistance; that is, velocity-independent resistance to passive movement not solely reflecting failure to relax (ie, distinct from spasticity or paratonia). Although the cogwheel phenomenon is often present (and may reflect tremor incidentally felt while assessing tone), isolated "cogwheeling" without "lead-pipe" rigidity does not fulfill minimum requirements for rigidity.

Rest Tremor

Rest tremor refers to a 4- to 6-Hz tremor in the fully resting limb, which is suppressed during movement initiation. Rest tremor can be assessed during the entire interview and examination (MDS-UPDRS 3.17, 3.18). Kinetic and postural tremors alone (MDS-UPDRS 3.15 and 3.16) do not qualify for parkinsonism criteria.

Note: In PD, a parkinsonian rest tremor in the hand also can be observed with prolonged posture (ie, "re-emergent" tremor); however, to meet criteria, tremor also must be observed during rest. In patients with associated postural or kinetic tremor, care must be taken to ensure that the limb is fully relaxed during examination. The frequency of a true rest tremor usually will be slower than the associated action tremor

Although postural instability is a feature of parkinsonism, it is not part of the MDS-PD criteria for parkinsonism caused by PD. Postural instability often

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

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 MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Supportive criteria
(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
☐ 2. Presence of levodopa-induced dyskinesia
☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:

☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, 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, defined according to consensus criteria[31] within the first 5 y of disease
☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
☐ 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 (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Red flags

☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
☐ 3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
   a) Orthostatic hypotension[32]—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 in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. 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)
☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

Criteria Application:

1. Does the patient have parkinsonism, as defined by the MDS criteria? If no, *neither* probable PD nor clinically established PD can be diagnosed. *If yes:*	Yes ☐	No ☐
2. Are any absolute exclusion criteria present? If "yes," *neither* probable PD nor clinically established PD can be diagnosed. *If no:*	Yes ☐	No ☐
3. Number of red flags present ____		
4. Number of supportive criteria present ____		
5. Are there at least 2 supportive criteria *and* no red flags? If yes, patient meets criteira for **clinically established PD**. *If no:*	Yes ☐	No ☐
6. Are there more than 2 red flags? If "yes," probable PD *cannot* be diagnosed. *If no:*	Yes ☐	No ☐
7. Is the number of red flags equal to, or less than, the number of supportive criteria? If yes, patient meets criteria for **probable PD**	Yes ☐	No ☐

occurs in later stages of PD, but its presence early in disease suggests an alterative diagnosis.[15]

Diagnostic Criteria for PD

Having established that the patient has parkinsonism, the MDS-PD criteria will be applied to determine whether the patient meets criteria for PD as the cause of this parkinsonism.

Diagnosis of clinically established PD requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria
3. No red flags

Diagnosis of clinically probable PD can be made in:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria, ie, if one red flag is present there must also be at least one supportive criterion; if two red flags, at least two supportive criteria are needed. If there are more than two red flags, clinically probable PD cannot be diagnosed.

Supportive Criteria

1. Clear and dramatic beneficial response to dopaminergic therapy. To meet this criterion, during initial treatment, patients should have returned to normal or near-normal level of function.In the absence of clear documentation of initial response (eg, initial treatment with lower-efficacy agents or very low dose), a dramatic response also can be classified as:
   a. Marked improvement with dose increases or marked worsening with dose decreases. Mild changes with dose changes do not qualify. This can be documented either objectively (defined as >30% in UPDRS III with change in treatment), or subjectively with a clear history of marked changes provided by a reliable patient or caregiver.
   b. Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

Note: To meet this criterion, it is not sufficient to document some beneficial response to dopaminergic therapy; the response must be unequivocal and of large amplitude. If treatment response is of modest amplitude, the patient does not meet this criterion. The requirement of predictable end-of-dose wearing off is to ensure that these are true dopaminergic fluctuations (as opposed to day-to-day variability, for example). The documentation of predictable end-of-dose wearing off can be from retrospective history (ie, patients do not have to currently be experiencing predictable fluctuations).

2. Presence of levodopa-induced dyskinesia
3. Rest tremor of a limb, documented on clinical examination (in the past, or on current examination)*Note: This is included primarily for two reasons: (1) rest tremor is less common in alternate conditions, and (2) rest tremor may occasionally be less responsive to therapy; if so, criterion 1 may be harder to meet in tremor-predominant PD.*
4. Positive results from at least one ancillary diagnostic test having a specificity greater than 80% for differential diagnosis of PD from other parkinsonian conditions. Currently available tests that meet this criterion include:
   - Olfactory loss (in the anosmic or clearly hyposmic range, adjusted for age and sex)
   - Metaiodobenzylguanidine scintigraphy clearly documenting cardiac sympathetic denervation

Note: To meet these criteria, the marker must have been demonstrated to provide more than 80% specificity in most studies (with a minimum of three studies from different centers).

Absolute Exclusion Criteria

For all absolute exclusion criteria and red flags, the criterion is assumed to not be met because of an alternate unrelated cause. For example, unilateral cerebellar abnormalities attributable to a cerebellar hemisphere stroke, or a wheelchair-bound state attributable to spinal cord injury would not necessarily be exclusion criteria.

The presence of any of these features rules out PD:

1. Unequivocal cerebellar abnormalities on examination, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, 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, defined according to consensus criteria[31] within the first 5 y of disease
   Note: This refers specifically to the frontotemporal type of dementia, which is associated with disorders other than PD (tau deposition disorders, and so forth). Other forms of dementia are not an exclusion criterion for PD. Also note that for this criterion, and for all other criteria with a time component, waiting until the disease duration is 5 y before the criterion is considered as not met is not necessary (ie, if the patient has a 4-y disease duration without frontotemporal dementia and all other criteria are met, this criterion is not met, and one can still diagnose clinically established PD).

4. Parkinsonian features restricted to the lower limbs for more than 3 y
5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
   Note: In application of this criterion, clinical judgment should be applied. For example, if a patient received only a low-dose "highly-atypical" neuroleptic, the evaluator may consider this treatment inconsistent with drug-induced parkinsonism. Or, if parkinsonism clearly persists long after complete medication withdrawal, the investigator might conclude that the dopamine blocker unmasked subclinical PD.
6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
   Note: To meet this criterion, patients must have received a sufficiently high dose of levodopa daily (≥600 mg/d). For patients who are untreated, or who have received less than 600 mg levodopa, this criterion cannot be applied. Absence of treatment response should be clearly reported by patient (or reliable witness) or if sequential examinations are available, can be confirmed objectively (ie, improvement ≤3 points on the MDS-UPDRS Part III). Because mild parkinsonism and tremor may be less clearly responsive to therapy, the patient also must have at least moderate severity parkinsonism (ie, MDS-UPDRS score >2 of one measure of rigidity or bradykinesia) to meet this criterion.
7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
8. Normal functional neuroimaging of the presynaptic dopaminergic system
   Note: This criterion does NOT imply that dopaminergic functional imaging is required for diagnosis (nor does the task force wish to imply that this should be performed in diagnosing PD). If no imaging has been performed, this criterion does not apply.
9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or the expert evaluating physician, based on the full diagnostic assessment, believes that an alternative syndrome is *more likely* than PD.
   Note: This criterion includes not only rare conditions that can mimic PD, but also can include the more common alternative parkinsonian syndromes (MSA, PSP, and so forth). Note again that dementia with Lewy Bodies is not considered an alternative parkinsonian syndrome according to this criterion.

Red Flags

1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
2. A complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment
   Note: This criterion is targeted at patients who may have been misdiagnosed with parkinsonism. This must be defined based on observation (ie, historical information cannot suffice). The absence of progression must be continuous over a minimum of 5 years.
3. Early bulbar dysfunction, defined as one of **severe** dysphonia, dysarthria (speech unintelligible most of the time), or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within the first 5 y of disease.
   Note: Severity definitions are from the MDS-UPDRS[30] (ie, 4 for dysarthria, ≥3 for dysphagia).
4. Inspiratory respiratory dysfunction defined as either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5. Severe autonomic failure in the first 5 y of disease. This can include:
   a. Orthostatic hypotension[32]: 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
   b. Severe urinary incontinence or urinary retention in the first 5 y of disease (excluding long-standing low-volume stress incontinence in women), which is not simply functional incontinence (ie, inability to get to the bathroom in a reasonable time). In men, urinary retention must not be caused by prostate disease, and this must be associated with erectile dysfunction.
      Note: Autonomic dysfunction is a common feature of PD; however, this criterion is intended to identify the severe autonomic dysfunction associated particularly with multiple system atrophy. If the patient has more than 5 y disease duration at assessment, these features must have occurred within the first 5 y (documented either by chart review for orthostatic hypotension or by a clear onset time on history for urinary incontinence).
6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset. *Note: For this criterion, falls are considered to be attributable to impaired balance, implying that falls attributable to loss of consciousness (syncope, seizure), or to situations during which persons with normal balance would*

also fall (athletic activities, violence, slipping on ice, and so forth) are not included. Clinical judgment is required to determine whether impaired balance played a key role in the fall.

7. The presence of disproportionate anterocollis (dystonic in nature) or contractures of hand or feet within the first 10 y.
8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include:
   - Sleep dysfunction: sleep-maintenance insomnia, excessive daytime somnolence, symptoms of rapid eye movement sleep behavior disorder
   - Autonomic dysfunction: constipation, daytime urinary urgency (ie, not simply nocturia), symptomatic orthostasis
   - Hyposmia
   - Psychiatric dysfunction: depression, anxiety, or hallucinations

   Note: This criterion is designed primarily to detect nonparkinsonian conditions mimicking PD (eg, subjects without evidence of dopaminergic deficit, dystonic tremor, essential tremor)
9. Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry in the more affected limb, and isolated extensor plantar response).

   Note: Mild reflex asymmetry is excluded because it can commonly be seen in PD. Isolated extensor plantar response is excluded because of the difficulty in differentiating this from a "striatal toe" (an occasional finding in PD), and the possibility that unrelated pathology (eg, mild cervical myelopathy) can produce this finding.
10. Bilateral symmetric parkinsonism throughout the disease course. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination.

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