

Early Diagnosis of Parkinson's Disease: Recommendations From Diagnostic Clinical Guidelines

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Abstract

Therapeutic options for Parkinson's disease (PD) are currently limited to symptomatic agents. Levodopa is the most efficacious treatment; however, higher doses and long-term use are associated with adverse effects such as motor fluctuations and dyskinesia. Early treatment of PD with other agents such as dopamine agonists and monoamine oxidase type B inhibitors can provide symptomatic benefit and delay initiation of levodopa therapy. Early treatment of PD is contingent upon early and accurate diagnosis of the disease, which can be challenging because there are no biomarkers or neuroimaging or other clinical tests available to confirm the diagnosis. PD diagnosis is currently based on the presence or absence of various clinical features and the experience of the treating physician. A definitive diagnosis can be made only after autopsy. Moreover, the signs and symptoms present in early PD can resemble those of a number of other movement disorders, particularly other forms of parkinsonism, such as multiple system atrophy, drug-induced parkinsonism, and vascular parkinsonism, as well as diffuse Lewy body disease and essential tremor. Nevertheless, diagnosis of PD based on clinical features and response to antiparkinsonian medication can be achieved with a fairly high level of accuracy, particularly when made by a physician specializing in movement disorders. This article reviews and summarizes published recommendations for the clinical diagnosis of PD.

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For author information and disclosures, see end of text.

Introduction

Parkinson's disease (PD) is a disabling neurodegenerative disorder with a prevalence rate estimated as high as 329 per 100,000 persons in the United States.¹ The annual incidence rate has been estimated to range from 16 to 19 per 100,000 persons when the diagnosis is made by a movement disorder specialist.² PD primarily affects people over the age of 50 years, and prevalence and incidence rates increase with age. Therefore, aging of the general population is likely to result in a dramatic increase in the number of people diagnosed with PD. One study projected that by the year 2030, the number of people over the age of 50 (and consequently the number of persons with PD) will double, resulting in an estimated 9 million persons with PD worldwide.³

Although there is currently no cure for PD, and the therapeutic armamentarium is limited to symptomatic agents, appropriate and timely treatment has been shown to have a beneficial effect on the course of the disease.⁴⁻⁶ The most efficacious therapeutic agent for PD is levodopa, which is converted to dopamine through decarboxylation.⁷ Although levodopa is the gold standard in the treatment of PD, its use is often delayed to avoid the early development of motor fluctuations and dyskinesia. In early, mild PD, therapy is often initiated with a monoamine oxidase type B (MAO-B) inhibitor or a dopamine agonist, reserving the use of levodopa until functional impairment is more significant.^{6,8}

Multiple studies have demonstrated that dopamine agonists have a mild-to-moderate benefit on PD motor symptoms.^{7,8} In addition, several studies have demonstrated that the early use of dopamine agonists can delay the need for levodopa and, consequently, the development of motor fluctuations and dyskinesia.^{4,7} However, dopamine agonists can be associated with bothersome adverse events, including hallucinations, pedal edema, impulse control disorders, and daytime sleepiness. Data also support the early use of MAO-B inhibitors for early PD motor symptoms. Although MAO-B inhibitors are usually less effective than levodopa or dopamine agonists, they are associated with significantly fewer adverse events.^{4,6,9,10} Early treatment of PD improves motor symptoms, but may also ameliorate nonmotor symptoms, such as depression, and can enhance patients' quality of life (QOL).¹¹ Moreover, third-party payer data suggest that early treatment of PD is a cost-effective strategy.¹²

The effects of early treatment can be significant but are contingent upon timely and accurate identification of the disease. Several guidelines are available to help clinicians recognize the signs and symptoms of PD and to provide insight and recommendations for differential diagnosis. Despite the availability of clinical guidelines, underdiagnosis and misdiagnosis of PD is quite common. Among general neurologists, Hughes et al found that nearly 24% of PD diagnoses were incorrect (when confirmed by autopsy), with the most common misdiagnoses including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and Alzheimer's disease.¹³

A population-based study using the United Kingdom Parkinson's Disease Society Brain Bank criteria found that at least 15% of patients diagnosed with PD were misdiagnosed, whereas 19% of those who did have PD were inaccurately diagnosed with a different disorder.¹⁴ In contrast, Jankovic et al examined data in 800 patients with PD enrolled in a clinical trial for early treatment. These patients were reexamined 6 years after the initial diagnosis by a neurologist specializing in movement disorders, and only 8% of the initial diagnoses were incorrect. In other words, initial diagnoses by a movement disorder specialist were accurate in 92% of cases.¹⁵

Although there are several clinical practice guidelines for the diagnosis and treatment of PD, studies indicate that they are underutilized by healthcare professionals treating PD. A German study found that only 53% of 181 private practice neurologists were aware of clinical practice guidelines for the diagnosis of PD.¹⁶ In addition, it was demonstrated that those who were aware of the guidelines for PD had significantly greater knowledge regarding the differential diagnosis and treatment of PD. Another German study reported that 88% of 213 private practice neurologists were aware of PD-specific guidelines; more than 90% of those who were aware of the guidelines reported that they were beneficial and used them in clinical practice.¹⁷ In the United States, practice patterns by physicians and nonphysician providers such as nurse practitioners and physician assistants in the treatment of PD were in agreement with recommended clinical guidelines only about half of the time.¹⁸ Moreover, physicians were 3 times less likely than nonphysician providers to refer patients to a specialist for confirmation of a PD diagnosis.¹⁸

In the United States, the primary guidelines for diagnosing PD are those published by the American Academy of Neurology (AAN).¹⁹ This article reviews recommendations from the AAN, as well as 2 other comprehensive guidelines for PD that originate from the United Kingdom: (1) the clinical guidelines published by the Royal College of Physicians and produced by the National Collaborating Centre for Chronic Conditions (NCCCC), which is funded by the National

■ **Table.** United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

Step 1: Parkinsonian syndrome diagnosis

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least 1 of the following:
 - Muscular rigidity
 - 4- to 6-Hz rest tremor
 - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2: Parkinson's disease exclusion criteria

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumor or communicating hydrocephalus on computed tomography scan
- Negative response to large doses of levodopa (if malabsorption is excluded)
- MPTP exposure

Step 3: Positive criteria for Parkinson's disease

(3 or more required for definite Parkinson's disease diagnosis)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70%-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

MPTP indicates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Reprinted with permission from Hughes AJ, et al. *J Neurol Neurosurg Psychiatry*. 1992;55(3):181-184.

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Institute for Health and Clinical Excellence, and (2) the clinical guidelines produced by the Scottish Intercollegiate Guidelines Network (SIGN).^{20,21} Also discussed are the most widely used diagnostic criteria for PD—those defined by the United Kingdom Parkinson's Disease Society Brain Bank.^{13,19}

Definitions and Diagnostic Criteria

The criteria for diagnosis of PD set forth by the United Kingdom Parkinson's Disease Society Brain Bank consists of 3 diagnostic steps (Table):

1. Determining whether a patient's symptoms fall within the broader category of parkinsonism (defined as presentation of bradykinesia in addition to muscular rigidity, 4- to 6-Hz rest tremor, or postural instability unrelated to visual, vestibular, cerebellar, or proprioceptive dysfunction);
2. Ruling out those patients presenting with a spectrum of exclusion criteria; and
3. Including those patients presenting with specific positive criteria, any 3 of which, taken together, constitute a PD diagnosis after both stages 1 and 2 have been met.¹³

In the study by Hughes et al, in which only 76% of PD diagnoses were correct, the full extent to which the United Kingdom Parkinson's Disease Society Brain Bank criteria were being used by neurologists was unclear. Nevertheless, when the study authors applied the United Kingdom Parkinson's Disease Society Brain Bank criteria to 100% of these cases, albeit retrospectively, they observed that diagnostic accuracy increased to 82%. Confirmation of diagnoses was based on the pathologic finding of Lewy bodies.¹³ In a subsequent study, when United Kingdom Parkinson's Disease Society Brain Bank criteria were applied to 100 cases, there was 90% diagnostic accuracy as confirmed by autopsy.²² This degree of accuracy was as high as could be expected using diagnostic methods based entirely on clinical features.

The NCCCC guidelines are largely in agreement with the United Kingdom Parkinson's Disease Society Brain Bank criteria, noting that hypokinesia in addition to bradykinesia is a common PD sign, along with rest tremor and rigidity.²¹ The NCCCC guidelines note that initial symptoms will typically be unilateral, and symptoms will likely become bilateral over time. The authors added, however, that there is no single means of identifying PD, and that an absolutely definitive diagnosis can, at present, only be achieved postmortem with detection of Lewy bodies in brain tissue and catecholaminergic neuron degeneration.²¹

The Parkinson Study Group observed several features of patients misdiagnosed with PD that tend to separate them

from patients with early PD. Compared with patients with early PD, misdiagnosed patients presented with the following: (1) higher Hoehn and Yahr stage, (2) higher Unified Parkinson's Disease Rating Scale (UPDRS) scores for bradykinesia, (3) postural instability and gait difficulty as initial symptoms, and (4) lower tremor scores.¹⁵ Based on this study and several others, the AAN guidelines recommended that initial or early falling, poor response to levodopa, symmetry at onset, rapid progression, lack of tremor, and dysautonomia should be used to distinguish PD from other forms of parkinsonism early in the disease course.¹⁹

Genetic Testing

The genetic contribution to the development of PD is, at present, unclear and has little, if any, bearing on the diagnosis or management of the disease. However, genetic associations with PD have been identified, and approximately 20% of patients with PD have a first-degree relative with the disease.²⁰ Genetic studies have identified at least 9 genes with mutations that may cause 10% to 15% of PD cases.²³ The leucine-rich repeat kinase 2 (LRRK2) and parkin mutations are the most studied.²⁰ LRRK2 occurs in 5% to 8% of patients with a first-degree family history compared with 0.4% to 1.6% without such a history. Parkin mutations are seen at a much higher frequency in patients with early-onset disease, but quite rarely in patients over the age of 30 years. The SIGN guidelines do not recommend routine genetic testing because interpretation of results is problematic, and the results do not guide treatment.²⁰

Uncertainty and Referrals for PD Diagnosis

Achieving a reliable PD diagnosis early in the course of the disease is often quite difficult. Thus, the clinical guidelines underscore the importance of clinicians continuing to evaluate their patients, whether they have already diagnosed a given patient with PD or are unsure of the diagnosis, and determining after repeated visits whether their diagnoses and assumptions are correct.¹⁹⁻²¹ The NCCCC guidelines suggest that patients with early and mild PD, whether or not they are receiving treatment, be reassessed every 6 to 12 months so clinicians can review their diagnosis and determine treatment needs. After treatment has been initiated, these guidelines suggest follow-up every 2 to 3 months.²¹

Noting the poor specificity of clinical diagnosis in early PD, the SIGN guidelines suggest caution on the part of clinicians when discussing a PD diagnosis with a patient.²⁰ It is also recommended that diagnosis be performed by a movement disorder specialist rather than a primary care practitioner (PCP), that such a diagnosis is performed prior to

treatment initiation, and that referral to a movement disorder specialist occurs without delay.^{20,21} The SIGN guidelines point out that in the Scottish primary care setting (which is likely comparable to that in the United States), the average PCP will see a new patient with PD once every 3.3 years, making it unlikely that a clinician would have an opportunity to develop refined diagnostic skills in PD.²⁰ The NCCCC guidelines report data indicating that community-based PCPs misdiagnose PD approximately 47% of the time, neurologists lacking expertise in movement disorders misdiagnose PD 25% of the time, and movement disorder specialists have a misdiagnosis rate between 6% and 8%.²¹

Differential Diagnosis

PD in its early stages can easily be mistaken for any number of disorders. PD is most likely to be confused with other forms of parkinsonism, such as MSA, PSP, corticobasal degeneration, and Lewy body dementia.²⁰ Other degenerative diseases, such as Alzheimer's disease and primary lateral sclerosis, can also be mistaken for PD, as can nondegenerative conditions, such as essential tremor, dystonic tremor, vascular parkinsonism, and drug-induced parkinsonism.

Clinical Features of PD Versus Other Forms of Parkinsonism

Apart from the clinical features previously described for PD diagnostic criteria, there are a number of additional clinical manifestations that can be useful in distinguishing PD from other conditions. Falls are a common clinical feature related to PD, and the onset of falling with respect to disease duration can be important in the differential diagnosis. A study in a group of patients with various forms of parkinsonism found that recurrent falls within the first year of initial symptom onset was predictive of a non-PD form of parkinsonism.²⁴ PD was found to have a much longer latency period (time from first symptoms to onset of recurrent falls) than MSA, dementia with Lewy bodies, corticobasal degeneration, and PSP.

Because MSA is commonly mistaken for PD, a detailed analysis of the differentiating features of the 2 conditions is particularly useful for diagnosis. Wenning et al examined 100 consecutive pathologically confirmed cases of PD and 38 pathologically confirmed cases of MSA from the United Kingdom Parkinson's Disease Society Brain Bank, to determine the specificity and sensitivity of various clinical features for differential diagnosis.²⁵ The mean age of patients in the MSA group was 55.9 years compared with 62.4 years in the PD group, and there was a significant difference in mean disease duration prior to death. MSA patients survived an average of 6.8 years after symptom onset compared with 13.2

years in patients with PD ($P < .0005$).²⁵ Initial modeling for diagnostic criteria was based on signs and symptoms recorded by investigators from the time of first patient encounter to their death. Subsequent modeling limited data to that from the first 5 years of symptom onset. Four clinical features were found to represent significant predictors of MSA compared with PD: (1) autonomic features present (defined as symptomatic postural hypotension, urinary urge incontinence, fecal incontinence, urinary retention requiring catheterization, or persistent erectile failure), (2) poor initial response to levodopa, (3) early motor fluctuations, and (4) initial rigidity. The presence of any 2 of these features provided a sensitivity of 87.1% and a specificity of 70.5% for distinguishing MSA from PD.²⁵

A total of 23% of patients with PD (based on the longer-term data) had a poor initial response to levodopa; although this percentage was much smaller compared with patients with MSA (58% poor initial response), it demonstrates the limitations of levodopa challenge in the absence of other clinical variables.²⁵ (See further discussion of drug challenge below.)

Another smaller study, also originating from the United Kingdom Parkinson's Disease Society Brain Bank, sought to identify clinical features that could be used to distinguish MSA, PD, and PSP.²⁶ The study compared 20 patients with pathologically diagnosed PD, 16 with pathologically diagnosed MSA, and 16 with pathologically diagnosed PSP. The investigators found that while no tremor was present at disease onset in 8 (40%) patients with PD, tremor was absent in 14 (88%) patients with MSA and in 10 (62%) patients with PSP. Orthostatic hypotension occurred in only 1 (5%) patient with PD, compared with 11 (69%) patients with MSA and none with PSP. Lack of response to levodopa occurred in 31% of patients with MSA and 75% of patients with PSP, whereas all of the patients with PD responded to levodopa.²⁶ Consistent with the Wenning et al²⁵ study, disease progression was considerably faster in MSA (and PSP) compared with PD, whereas symmetrical symptom onset was a feature particularly common in patients with PSP.

Drug Challenge

Acute challenge testing with levodopa or apomorphine is a long-used method for diagnosing PD. The clinical treatment guidelines are divergent on the question of the utility of drug challenge for PD diagnosis. The AAN guidelines recognize the acute challenges as a valid diagnostic test when there is doubt about the diagnosis; however, they also highlight the approximately 30% chance of a false negative and the 20% to 30% chance of a false positive. In contrast, the NCCCC and SIGN guidelines regard acute levodopa and apomorphine

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challenges as lacking clinical merit. The AAN recommendations are based, in part, on data from Merello et al, who studied 82 symptomatic patients without a specific diagnosis who were given acute levodopa challenge and followed for 24 months. An improvement of 30% with the challenge was considered a positive response. When patients were stratified by UPDRS score, those with a score of 10 or less could be diagnosed with PD with a sensitivity of 71% and a specificity of 100%. However, for those with UPDRS scores of 21 or greater, sensitivity was reduced to 36% and specificity to 87%.²⁷

The AAN guidelines also cite an Italian study in which 134 patients (83 with a clinical PD diagnosis, 28 with MSA, 6 with PSP, and 17 with unclassified parkinsonism) were given acute challenge with levodopa and apomorphine.²⁸ Motor response was evaluated by UPDRS score 1 hour after administration of levodopa and 20 minutes after each subcutaneous administration of apomorphine. Patients with PD had significantly better UPDRS scores than the other patients for both drug challenges, regardless of the dose administered (all, $P < .001$). Levodopa challenge had a sensitivity of 77% and a specificity of 71%, while apomorphine challenge (4.5-mg dose) yielded a sensitivity of 76% and a specificity of 67%.²⁸

In summary, the specific utility of acute levodopa and apomorphine challenge, according to the AAN guidelines, is for confirming an uncertain PD diagnosis, although the guidelines also note a lack of data regarding any advantage over clinical diagnostic criteria.¹⁹ The NCCCC and SIGN guidelines advise against using acute levodopa and apomorphine challenge for differential diagnosis, noting that these methods do not add any more diagnostic information than chronic use of levodopa.^{20,21} Both of these guidelines also point out the adverse events associated with acute levodopa challenge (eg, neuropsychiatric effects, postural hypotension) and apomorphine challenge (drowsiness, nausea, vomiting, hypotension, sweating), and the risk to patients, particularly older patients or those with cognitive dysfunction.^{20,21}

Smell Testing

The frequency of olfactory impairment in PD provides an opportunity for differential diagnosis, although this particular dysfunction occurs to some extent in many parkinsonian patients. The AAN guidelines support consideration of olfactory testing for differentiation between PD and PSP, as well as PD and corticobasal degeneration, but not for differentiation of PD and MSA. Olfactory testing was associated with a diagnostic sensitivity of 77% and a specificity of 85%.^{19,29} The 2 UK guidelines recommend against olfactory testing in the clinical setting.^{20,21}

Imaging

Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) imaging uses a radiolabeled compound as a probe of dopamine transporters to study the progression of presynaptic dopaminergic degeneration. The AAN guidelines indicated that SPECT may be useful in differentiating PD from essential tremor but indicated that there was insufficient evidence to determine if SPECT is useful to differentiate various forms of parkinsonism.¹⁹ The NCCCC guidelines expressed ambivalence regarding the use of SPECT, but cited studies that support its use in differentiating essential tremor from dopaminergic deficiency in patients with upper limb postural or action tremor.²¹ The NCCCC further stated that SPECT may eventually be useful in distinguishing drug-induced and psychogenic parkinsonism from a state of dopaminergic deficiency. The SIGN guidelines support the use of SPECT to distinguish PD from nonneurodegenerative parkinsonism and tremor disorders, but not from neurodegenerative forms of parkinsonism.²⁰

Magnetic Resonance Imaging

The AAN guidelines found magnetic resonance imaging (MRI) to possibly be useful in differentiating PD and MSA.¹⁹ The NCCCC guidelines regard structural MRI as potentially useful for differential diagnosis of PD from other forms of parkinsonism if conducted by an expert practitioner, but recommends against its diagnostic use otherwise.²¹ The SIGN guidelines recognize MRI as a useful tool for evaluating cerebrovascular disease to differentiate idiopathic PD from vascular parkinsonism. MRI is effective for measuring the extent of brain atrophy and to determine the presence of structural lesions that can be associated with parkinsonism, but SIGN advocates against the use of MRI for diagnosis of idiopathic PD.²⁰

Sonography

Transcranial sonography is not supported in the SIGN guidelines for differential diagnosis, whereas the AAN and NCCCC find insufficient data to make a recommendation.^{19,21}

Positron Emission Tomography

None of the guidelines supports the use of positron emission tomography for differential diagnosis in PD.^{19,21}

Conclusions

An early and accurate diagnosis of PD is critical to developing the most appropriate treatment strategy to maintain the best QOL for as long as possible. Unfortunately, the early recognition of PD can be challenging as there are other movement

disorders, such as MSA, PSP, drug-induced parkinsonism, vascular parkinsonism, and essential tremor, which can initially appear very similar to PD. Several guidelines have been published to assist in the accurate diagnosis of PD. Studies have shown that these guidelines are often underutilized; however, when used, they do appear to improve diagnostic accuracy. As there are no definitive clinical tests to confirm PD at this time, the most accurate PD diagnosis has been shown to come from a neurologist specializing in movement disorders. Although the published guidelines are not in complete agreement, when used by a physician experienced in the diagnosis and treatment of PD, levodopa or apomorphine challenges, olfactory testing, and various neuroimaging techniques may have some utility in the diagnosis of PD. Improved awareness of the clinical features of PD and differential diagnosis, as well as knowledge of and appropriate application of diagnostic aids, will allow clinicians to more accurately diagnose and treat early PD.

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