Prodromal and Early Parkinson’s Disease Diagnosis

Earlier diagnosis may lead to earlier and more effective treatments.

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Since its initial description in 1817,¹ the diagnosis of Parkinson’s disease (PD) has focused on motor impairment. Currently accepted diagnostic criteria²,³ require the presence of bradykinesia and at least 1 other motor sign, such as cogwheel rigidity or rest tremor; in this article, we refer to this as motor-PD. However, there is increasing recognition that neurodegeneration begins decades before the appearance of motor signs, often with the development of nonmotor symptoms such as hyposmia and sleep disturbances. Braak staging of PD (Figure) posits the spread of Lewy pathology in a caudal to rostral pattern. In this model, stages 1 and 2 represent early pathology in the olfactory bulb and brainstem, producing prodromal symptoms. Stage 3 represents involvement of the substantia nigra to produce motor symptoms. Stages 4 to 6 indicate increasing degrees of cortical involvement, associated with increasing rates of psychosis and dementia. The long latent phase of PD, termed prodromal-PD, represents an opportunity for early recognition of incipient PD. Such early recognition could allow not only better prognostic counseling but also initiation of possible neuroprotective therapies at a stage when therapies might be most effective. Here, we review the approach to prodromal and early PD, with an emphasis on tests and maneuvers that have a high diagnostic yield for the general neurologist.

Prodromal Symptoms

Prodromal-PD⁴ refers to the stage at which individuals do not fulfill diagnostic criteria for PD (ie, bradykinesia and at least 1 other motor sign) but do exhibit signs and symptoms that indicate a higher than average risk of developing motor symptoms and a diagnosis of PD in the future. Most prodromal symptoms are nonmotor and have a major impact on quality of life both for patients with prodromal-PD and for those whose disease stage has progressed to motor-PD. Thus, early detection and treatment of these prodromal symptoms is essential for high-quality care. The best-characterized symptoms of prodromal-PD include hyposmia, constipation, mood disorders, and REM sleep behavior disorder (RBD).

Hyposmia

Olfaction is impaired in up to 90% of patients with PD at the time of motor-PD diagnosis.⁵ Hyposmia is thought to be related to Lewy pathology in the olfactory bulb (Braak stage 1), which likely begins several years before the onset of motor symptoms. It is important to note that the majority of hyposmic individuals with PD are unaware of their deficit⁶; therefore, objective testing is necessary to detect hypos-
mia. Olfactory loss may be measured in multiple ways, including odor identification, odor detection, and odor discrimination; impairment in any of these is correlated with an increased risk of developing motor-PD.

A number of bedside tests for hyposmia and micros
mia have been developed. In a busy clinical setting, the most feasible of these may be the 12-item Brief Smell Identification Test (B-SIT), which is based on the 40-item University of Pennsylvania Smell Identification Test. This is a forced multiple-choice scratch-and-sniff test that measures a person’s ability to identify odors. The B-SIT reliably discriminates between people with and without motor-PD. The B-SIT may be self-administered by cooperative patients. Another test for assessing olfaction is the Sniffin’ Sticks test, a 16-item test incorporating odor threshold, discrimination, and identification. Sniffin’ Sticks may be more sensitive for the detection of hyposmia in prodromal-PD but requires a trained examiner to administer the test. For all tests of hyposmia, published normative values vary by age and sex. Hyposmia is a sensitive although nonspecific symptom, especially in individuals with a history of smoking, allergic rhinitis, or nasal polyps. However, the negative predictive value of a normal test result and relative ease of assessment make it an attractive initial screening tool for prodromal-PD.

**Constipation**

Another commonly noted feature of prodromal-PD is constipation, which may be related to Lewy pathology in the dorsal motor nucleus of the vagus nerve and the enteric nervous system (Braak stage 1). After adjustment for confounders, individuals with fewer than 1 bowel movement per day have approximately 3 times higher odds of developing motor-PD compared to individuals with more frequent bowel movements. Constipation is apparent as early as 20 years before the diagnosis of motor-PD, making it 1 of the earliest recognizable prodromal features. Like olfactory loss, however, constipation is nonspecific and may have myriad causes, especially in the elderly population. The positive predictive value of constipation is therefore too low to be used in isolation as a marker of prodromal-PD.

**Mood Disorders**

Mood changes are common in PD and are often noted prior to the onset of motor symptoms, possibly due to involvement of the serotonergic raphe nuclei and the adrenergic locus ceruleus (Braak stage 2). For instance, individuals with prescriptions for anxiolytics or higher anxiety scores on the Minnesota Multiphasic Personality Inventory have an increased risk of PD, lending support to the anecdotal concept of a premorbid-parkinsonian personality characterized by risk aversion and neuroticism. Retrospective case-control analysis of a population-based study from Rotterdam suggests that both anxiety and depression become significantly more common in patients only about 1 to 2 years before PD diagnosis. Thus, mood disorders may be a relatively late preclinical marker of impending motor-PD. As with constipation and hyposmia, however, mood disorders are too nonspecific to be used in isolation for the diagnosis of prodromal-PD.

**REM-Sleep Behavior Disorder**

RBD is 1 of the best-studied features of prodromal-PD and is associated with the highest risk of phenocconversion to motor-PD. Cohort studies indicate that between 50% and 70% of individuals with polysomnography-confirmed RBD will progress to develop a synucleinopathy (PD, dementia with Lewy bodies, multiple systems atrophy) within an average of 5 to 10 years. Within the cohorts studied, the risk of idiopathic PD (often with prominent cognitive impairment) and dementia with Lewy bodies was approximately 50%; a small minority of patients were ultimately diagnosed with multiple systems atrophy. Dream enactment symptoms of RBD typically involve vocalizations or movements of the upper extremities and may lead to inadvertent injury to the patient or his or her bed partner. Patient-reported questionnaires have been developed for identification of individuals with RBD, but similarly to patients with hyposmia, patients with RBD are typically not aware of their symptoms. Accurate collateral history from a bed partner is usually sufficient to make the diagnosis. In questionable cases or for individuals without bed partners, polysomnography can be obtained. Given the high risk of progression to a neurodegenerative syndrome, appropriate workup of suspected RBD is imperative.

**Predictive Value of Prodromal Symptoms**

A number of prodromal symptoms in patients with PD have been identified. Of these, RBD appears to have the highest positive predictive value, whereas hyposmia, constipation, and mood disorders are relatively sensitive but nonspecific when considered in isolation. However, in a report from the population-based Honolulu-Asia aging study, the combination of more than 2 prodromal symptoms predicted a 4 times higher incidence of PD than a single prodromal feature. Individuals with any 1 of these symptoms can be queried regarding other features consistent with prodromal-PD. A combination of these symptoms may be used to identify individuals at higher risk of motor-PD who can then be assessed further with more advanced or refined tools. Better defining these high-risk cohorts will be useful for recruiting subjects for studies to identify imaging and other diagnostic biomarkers.
Early Motor Features of Parkinson’s Disease

According to the Braak hypothesis, once Lewy bodies have propagated into the substantia nigra (Braak stage 3), motor symptoms appear. Current diagnostic criteria for PD (Table) require bradykinesia plus either rigidity or tremor. Although postural instability is also a core feature of PD, early falls should alert the examiner to the possibility of an atypical parkinsonian syndrome such as progressive supranuclear palsy (PSP). It is important to be familiar with the core motor features of early PD and and be able both to detect early PD and distinguish it from common mimics.

Bradykinesia

Both the UK Brain Bank and the Movement Disorders Society criteria for PD emphasize bradykinesia as the central feature of motor-PD. Bradykinesia is defined as slow and/or decrementing (initially normal but becoming slower, smaller, or pausing with repetition) movements. Limb bradykinesia is commonly assessed by asking the patient to perform a variety of tasks, including finger tapping, hand opening and closing, pronation-supination, toe tapping, and foot stomping. These tests should be performed and assessed independently with each limb for at least 10 seconds. Bradykinesia caused by PD is usually unilateral at the onset of motor symptoms; even when it is bilateral, it is usually asymmetric. Bradykinesia, including early complaints of micrographia or difficulty buttoning clothing, can have a significant impact on a patient’s daily living activities. Nondecrementing hypokinesia should alert the clinician to the possibility of an atypical parkinsonian syndrome. Although bradykinesia may be seen in the face (hypomimia) or voice (hypophonia), only limb bradykinesia is included in the diagnostic criteria for PD.

Rigidity

Rigidity is defined as velocity-independent passive resistance to movement. Rigidity in PD is typically cogwheeling, with a ratchet-like quality. Subtle rigidity can be enhanced by asking the patient to open and close the contralateral hand, known as Froment’s maneuver. Reduced arm swing is considered to be more closely associated with rigidity than bradykinesia. Like bradykinesia, the rigidity of PD is unilateral at the onset of motor symptoms and usually remains asymmetric throughout the disease course. Symmetric rigidity or spasticity should raise the possibility of vascular parkinsonism or another atypical syndrome.

Tremor

The classic tremor of PD is a moderate frequency, low-to-moderate amplitude resting tremor (see Evaluation of Patients With Tremor on p. 58). This is commonly assessed by asking the patient to sit with her or his arms supported (ie, in his or her lap or on the armrests of a chair) and perform a complex cognitive task, such as serial 7s or the months of the year in reverse. Parkinsonian tremor may also be reemergent, appearing after a patient has held a posture for a few seconds. However, appearance of tremor immediately on assuming a posture suggests an alternate etiology, such as essential tremor or dystonia. PD tremor may also be present in the jaw or lip, although this has also been described with essential tremor. Some patients without visible tremor may complain of an internal vibratory sensation before tremor is observable by the patient or examiner.

Postural Instability

The final core feature of idiopathic PD is postural instability. Most commonly, this is assessed by the pull test wherein the examiner stands behind the patient and exerts a sudden backwards tug; a normal response is a rapid recovery in 1 to 2 steps. It should be noted, however, that frequent falls within the first few years of symptoms should be considered a red flag feature for progressive supranuclear palsy or another atypical syndrome rather than idiopathic PD. Patients with impaired postural reflexes and freezing should be referred to physical therapy, as gait is often less responsive than other symptoms to medications.

Red Flags and Mimics

When assessing a patient with possible idiopathic PD, the examiner should be aware of alternative causes of parkinsonism. Commonly encountered exclusion criteria and red flags are listed in the Table. The second most common cause of parkinsonism, after idiopathic PD, is drug-induced parkinsonism (DIP), which can occur after exposure to dopamine-blocking drugs (eg, antipsychotics, antiemetics, antidepressants, gastrointestinal prokinetics) or, less commonly, with a variety of drugs including lithium, valproic acid, and amiodarone. After discontinuation of the offending agent, symptoms may improve but sometimes do not completely reverse. Evidence of neurodegeneration on dopamine functional imaging in more than 20% of patients with suspected DIP suggests that dopamine blockade can act as a chemical stress test that unmasks underlying incipient PD. Consistent with this idea, patients with DIP who have abnormal results on dopamine imaging manifest more prodromal nonmotor symptoms, including hyposmia. The development of so-called lower-extremity parkinsonism in an elderly individual with vascular risk factors should alert the clinician to the possibility of vascular parkinsonism.

Other degenerative atypical parkinsonian syndromes are less common than PD but can be difficult to distin-
Distinguish from PD, especially in the earliest stages. The atypical syndromes include multiple systems atrophy, usually with prominent cerebellar or autonomic features; progressive supranuclear palsy, which manifests as oculomotor abnormalities and early falls; corticobasal syndrome, classically apraxia, alien limb phenomena, or hemidystonia; and dementia with Lewy bodies, with early dementia and hallucinations. Atypical and secondary syndromes often do not have as robust and sustained of a response to treatment with levodopa as idiopathic PD; an empiric trial of levodopa can therefore be of both diagnostic and therapeutic utility. Clinicians should be mindful of these potential diagnoses as they assess any patient with parkinsonian symptoms.

Multimodal Screening Tools for Prodromal and Early Parkinson’s Disease

Given the mixed sensitivity and specificity of any 1 diagnostic tool for PD, effective screening algorithms must be multimodal. Most algorithms use a combination of prodromal symptoms and imaging or biochemical biomarkers to identify individuals at high risk of developing motor-PD. An innovative approach is taken by the PREDICT-PD study, which combines the presence of mood symptoms and/or RBD with results from smell testing, genotyping, and keyboard-tapping tasks to divide individuals into high-risk, middle-risk, and low-risk groups. A recently published interim analysis from this study after 3 years of follow-up showed a hazard ratio of 4.39 (95% confidence interval, 1.03-18.68) for the diagnosis of PD in the high-risk group compared to the low-risk group. If proven an effective screening tool, PREDICT-PD’s online algorithm can be readily deployed to reach populations without regular access to care from movement-disorder specialists. Predictive models have also been developed to identify subjects with a high risk of developing PD exclusively from administrative insurance diagnosis and procedure codes for constipation, hyposmia, and RBD. Models incorporating detailed administrative data together with demographic information are both sensitive and specific for PD.

The goal of these and other multimodal screening tools is to identify a population at significant risk of PD both to improve counseling for individual patients as well as to identify a potential population for clinical trials of disease-modifying agents at a stage where intervention is likely to be most effective. Thus, early recognition and diagnosis is crucial to the future of PD management. Although diagnostic criteria for prodromal-PD are still being developed and tested, it is reasonable to speculate that office-based olfactory testing might become a widely used screen in late middle-aged individuals; hyposmic patients could then be screened in further detail for pre-motor and motor symptomatology, or referred for specialty care as appropriate.

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