Improving Outcomes Through Early Diagnosis of Parkinson's Disease

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Abstract

Current diagnostic modalities in Parkinson's disease (PD) are limited by the fact that they identify PD by the presence of motor symptoms; by this point, over 60 percent of all dopamine neurons within specific regions of the basal ganglia may have been lost. Nonmotor symptoms manifest in PD long before motor symptoms, and the early presence of nonmotor symptoms offers an opportunity for early diagnosis and early treatment of PD, with consequent benefits to patient quality of life and potential treatment cost savings. Numerous different premotor symptoms have been identified; diminished olfactory function and REM behavioral sleep disorders (RBDs) may be particularly suitable for the purposes of early diagnosis. Olfactory testing, while in itself not specific for PD, has been shown to offer very high degrees of sensitivity and specificity in distinguishing PD from healthy controls and from other forms of parkinsonism, particularly when accompanied by other means of detection, such as sonography, motor symmetry evaluation, and magnetic resonance imaging (MRI)/diffusion tensor imaging. Biological biomarkers—including protein panels and autoantibody testing—have demonstrated excellent diagnostic capacity, and a recently identified 5-gene panel has been shown to have high specificity and sensitivity in distinguishing early PD from healthy controls and advanced PD. Increasingly sophisticated neuroimaging techniques are also proving capable of early PD detection and differentiation from other parkinsonian types. These recent developments in PD diagnosis underscore the necessity of rethinking what PD is and how, and when, it can be diagnosed.

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For author information and disclosures, see end of text.

Why Is Early Detection of Parkinson's Disease Important?

Although the exact prevalence of Parkinson's disease (PD) in the United States is difficult to accurately determine, one estimate puts the number of currently diagnosed US patients in excess of 645,000, a figure that does not include the many undiagnosed cases. If estimated undiagnosed cases are included, the figure climbs to approximately 849,000 people in the United States with PD.[1] The annual costs incurred for PD in the United States have been estimated at nearly $11 billion, including $6.2 billion in direct costs.[2] The largest proportion of costs incurred in PD occur in the later stages of the disease, when symptoms are at their most severe.[3] Thus, from a purely economic standpoint, any strategy that would maintain PD symptoms in the earlier stages of the disease (ie, fewer and less severe) would likely prove substantially beneficial toward limiting expenditures. From a patient quality-of-life (QoL) perspective, much the same is true. Considering that the effect of PD on patient QoL is one of the most severe of all chronic diseases, and because the most severe symptoms occur in more advanced disease, management strategies aimed at early detection and treatment have the potential to improve the experience of living with PD.[4]

Currently the diagnosis of PD relies on the clinician's recognition of motor symptoms and response to medication (eg, levodopa). However, by the time motor symptoms emerge, significant neurological damage has already occurred. Estimates vary as to the precise degree of neuronal loss required to produce symptomatic disease. Guttman et al found that an approximate loss of half of the dopamine neurons in the posterior putamen was required for symptoms to begin to manifest based on PET scans in patients with "early" PD, which is to say, patients who had already received a conventional diagnosis of PD when motor symptoms were clearly present.[5] In post-mortem studies, Pakkenberg et al found a reduction in neurons of 66% in the brains of 7 PD subjects compared with 7 matched controls.[6] A similar study, performed by Kish et al, found almost complete neuronal depletion in the putamen.[7] These figures describe a wide range, although it should be stated that the assumption is widely held that dopamine neuronal loss of 60% to 80% constitutes the threshold at which symptomatic disease occurs.[8] All of these data point to the fact that PD diagnosis by conventional means identifies a disease which is

Table 1. Indicators of Potential Misdiagnosis in PD[14,19-21]

Symptom symmetry
Absence of tremor
Severe axial or lower limb involvement, particularly early in disease
Frequent falls, particularly early in disease
Diffuse Lewy body disease
Rapid disease progression
Eye movement disorders
Early autonomic dysfunction (symptomatic postural hypotension, urinary urge incontinence, fecal incontinence, urinary retention requiring catheterization, or persistent erectile failure)
Unexpected/inappropriate (to PD) movement disorder (eg, myoclonus, tics, chorea)
Pyramidal or cerebellar dysfunction
Bulbar or pseudobulbar features
Parietal associative sensory disturbances
Apraxia (brain disorder causing inability to perform desired or requested movements)
Alien limb (involuntary/unconscious limb activity)
Severe cognitive deterioration or psychosis early in disease course
Limited efficacy of levodopa or apomorphine

PD indicates Parkinson's disease.

already advanced, and that any possibility of delaying disease progression, not to mention neuroprotection, may already be out of reach. The goal of slowing the progression of PD, preserving the neurophysiological integrity of the neurons, and thereby reaping the benefits in patient QoL with potential cost savings, is contingent upon diagnosing and treating PD well before the destructive structural changes have taken place. Treatment approaches in early PD is the subject of another article in this supplement. In the present article, we will focus on the value, practicality, and means of achieving early diagnosis in PD.

Misdiagnosis and Nondiagnosis in PD

PD, in the clinical setting, is commonly missed or misdiagnosed. A UK autopsy study of 100 subjects who had been diagnosed with PD found a misdiagnosis rate of 24%.[9] The likelihood of misdiagnosis appears to be strongly contingent upon who is doing the diagnosing and whether or not the clinician is applying diagnostic criteria from clinical guidelines—although application of the clinical criteria is still far from a guarantee of diagnostic accuracy. For example, when the Parkinson's Disease Society Brain Bank criteria were applied to subjects from the UK autopsy study previously discussed, the diagnostic accuracy improved from 76% to 82%.[10] When, in a later autopsy study, diagnosis was performed by a neuropathologist, the diagnostic accuracy improved to 90%.[11] The importance of who is undertaking a potential PD diagnosis is underscored by data showing that nearly half (47%) of PD diagnoses are incorrect when performed in the primary care setting, and specialists whose expertise is not specific movement disorders have an error rate of approximately 25%, while movement disorder specialists are mistaken in only 6% to 8% of cases.[12]

Many symptoms of PD are also common to other diseases both neurodegenerative and non-neurodegenerative in nature. Among neurodegenerative diseases, those most often confused with PD are multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), dementia with Lewy bodies, normal pressure hydrocephalus (NPH), and Alzheimer's disease.[13,14] Essential tremor is also a common source of confusion in PD diagnosis, although many of these patients will go on to develop PD.[15] Complicating the issue is the fact that drug-induced parkinsonism is very common and may constitute the second-most common cause of parkinsonism.[16-18]

A number of indicators of potential PD misdiagnosis have been identified, including rapid disease progression, a lack of asymmetry in symptoms, the presence of autonomic features such as postural hypotension, early postural instability, and poor initial response to levodopa.[14,15] Table 1 offers a list of some of the most common indicators of misdiagnosis.[14,19-21] It should be noted, however, that these indicators are suggestive rather than determinative, as evidenced, for example, by the fact that as many as 23% of people who prove to have PD fail to experience an initial positive response to levodopa.[20]

Achieving Early Diagnosis of PD

If early intervention to slow or halt disease progression in PD is to be achieved, it is necessary that the skills and resources for early detection of the disease become more refined and widely disseminated. This means that misdiagnosis of PD must become less common and that knowledge of the means of early detection of PD must become more widespread. At present, no single diagnostic test is available for PD, and accurate diagnosis—early or otherwise—has been a significant challenge, particularly among clinicians without particular expertise in movement disorders. The subjective nature of PD diagnosis, which relies on a group of physical and neurological assessments—none of which are, in themselves, diagnostically conclusive—has been an obstacle to accurate diagnosis. Nevertheless, the situation for PD diagnosis is improving and, recently, a number of new and diverse techniques for diagnosis, including early PD diagnosis, have been emerging and have the potential to considerably alter the diagnostic landscape.

Premotor Symptoms

Despite the reliance on motor symptoms for the standard diagnosis of PD, premotor symptoms hold promise for the early diagnosis of PD, and considerable progress has been made in recent years in establishing premotor symptoms as a means of identifying PD much earlier than in the past. One important observation—and one that may require rethinking certain assumptions about the fundamental nature of PD—is that PD is not simply a central nervous system (CNS) disease in which the peripheral nervous system (PNS) plays a minor part. Rather, there appears to exist a much larger role for the PNS than previously assumed, particularly in the early stages of the disease. Many of the premotor symptoms that arise in early PD emerge in PNS structures, such as the sympathetic cardiac plexus and vesicoprostatic plexus, and there is compelling evidence to suggest that PD actually begins in the PNS.[22,23]

The manifestations of premotor symptoms in PD are diverse, affecting olfactory structures, gastrointestinal and urinary function, and mood and sleep, as well as a variety of cognitive and autonomic functions. Gastrointestinal dysfunctions that manifest as premotor symptoms include gastroparesis and constipation. Urinary frequency, urgency, and nocturia constitute primary urinary dysfunctions in early PD. Sexual dysfunction in both men (erectile and ejaculation dysfunction) and women (poor vaginal lubrication and difficulty achieving orgasm) have also been observed as PD premotor symptoms. Mood disorders, including depression and anxiety, are well documented in the premotor phase, while sleep disturbances, including REM behavior disorder and excessive daytime sleepiness, are common premotor symptoms. Other nonmotor PD symptoms that may play a role in the premotor phase include pain, apathy, restless legs syndrome, fatigue, and poor ability to discriminate colors.[23]

Hyposmia, a well-known feature of PD,[24] may be the most notable of nonmotor symptoms observed in the premotor stage, in part because of the growing quantity of data demonstrating and explicating the role of olfactory loss in PD, but also because it may represent a highly useful means of achieving diagnosis of PD much earlier than has been possible up until the present. Indeed, a number of studies have sought, and are seeking, to determine its utility in PD diagnosis, with promising, if not yet fully utilizable, results. However, it should be noted that hyposmia is also associated with other conditions, including Alzheimer's disease and dementia with Lewy bodies, and thus the presence of hyposmia may be useful for the identification of persons at risk for PD, rather than being diagnostic of PD.[25]

One early study of olfactory function in parkinsonism (published in 1995), conducted by Wenning et al, employed the 40-odorant forced-choice University of Pennsylvania Smell Identification Test (UPSIT) to examine olfactory patterns in patients with idiopathic PD as well as several other parkinsonian syndromes, while also evaluating the utility of the UPSIT itself in this context. The patient population included 118 subjects with PD, 29 with MSA, 15 with PSP, and 7 with CBD.[26] The investigators found that compared with PSP, CBD, and MSA patients, PD patients scored significantly lower on the UPSIT. The UPSIT demonstrated a sensitivity of 77% and specificity of 85% in distinguishing PD from the atypical parkinsonian syndromes.[26] These results are certainly encouraging, if not conclusive, in positioning olfactory testing as a means of early PD detection.

A study from the United Kingdom recruited 18 PD patients, 14 patients with vascular parkinsonism (VP), and 27 matched controls, and compared their olfactory function using UPSIT.[27] The authors found a highly significant difference in UPSIT scores between PD and VP patients, and also between PD patients and controls (both $P < .0001$). There was no significant difference between the VP patients and controls. The authors found that the overall sensitivity of UPSIT was 86% and the specificity 89%. However, when the study subjects were divided into 2 age groups (65-75 and 76-88 years), UPSIT sensitivity and specificity in the younger group was 100% and 86%, respectively, compared with 86%

and 80%, respectively, in the older group.[27] It is conceivable that these results may have additional implications for early detection (if the younger group might be presumed to have, on average, less advanced disease), although these age-difference results may simply reflect the deterioration of olfactory function with advancing age.

A separate UK study employed UPSIT to compare 18 subjects with PD to 17 subjects with early-onset parkinsonism (EOPD) who possessed the PARK2 mutation (parkin-positive), 11 EOPD patients without PARK2 (parkin-negative), and 28 matched controls.[28] Highly significant differences in reduced scores were observed between the PD group and both the parkin-positive and health control groups (both $P < .0001$). The PD group scores were also significantly lower than the parkin-negative group, although the overall difference was less robust ($P = .046$).[28]

A recently published German study added an additional dimension to this area of interest by combining olfactory testing with sonography and motor symmetry evaluation in 632 patients with various types of early parkinsonism, including PD, VP, atypical parkinsonian syndromes, essential tremor, and major depressive disorder with motor slowing. Inclusion criteria allowed for subjects 35 years or older with a score of 3 or higher on the motor part of the UPDRS, and olfactory testing was conducted using a 12-item instrument called Sniffin' Sticks (SS-12). Motor asymmetry was determined by a 2-point or greater difference between the left and right scores on the side-specific elements of the UPDRS. Transcranial ultrasonography was used to measure hyperechogenicity, which was defined as .24 cm^2 or greater.[29] The authors arrived at several sets of results (sensitivity, specificity, and positive predictive value [PPV]) based on which of the 3 measures were included in the calculation, and which of the features (ie, hyposmia, motor asymmetry, hyperechogenicity) were present for each calculation. When only motor asymmetry and hyposmia were evaluated, and when both were present, the ability to discriminate between PD and other parkinsonism disorders was as follows: sensitivity, 64%; specificity, 84%; PPV, 92%. When only hyposmia and hyperechogenicity were evaluated, and both were present, the results were: sensitivity, 66%; specificity, 89%; PPV, 95%. When all 3 features were evaluated and 2 features were present, the results were: sensitivity, 96%; specificity, 72% (84% if VP was excluded); PPV, 91% (96% excluding VP). When all 3 features were evaluated and all were present, the results were: sensitivity, 57%; specificity, 94% (100% excluding VP); PPV, 97% (100% excluding VP).[29]

Further insight into the role of olfactory function is expected to be derived from the Parkinson's Associated Risk Study (PARS). PARS is a large-scale, long-term study funded by the Department of Defense, in which olfactory testing and neuroimaging is being applied to the first-degree relatives of PD patients with the hope that the results will allow for the development of a reliable PD screening tool. The study was started in 2006, and collection of primary outcome measure data is expected to be completed in November of 2013.[30]

Finally, it is worth noting several other nonmotor symptoms that may, ultimately, play a role in early PD detection. A survey of over 1000 PD patients by Barone et al observed 3 categories of nonmotor symptoms that appeared to arise early in the course of PD, prior to motor symptoms, and which may comprise early diagnostic markers for the disease: apathy, attention/memory, and psychiatric symptoms (including depression and anxiety).[31] The presence of REM sleep behavior disorder (RBD) may also play a role in early PD detection, as some studies have shown that up to 60% of patients with idiopathic RBD will develop PD or dementia with Lewy bodies.[25] Finally, the presence of Lewy bodies in the gastrointestinal tract may provide a means for early diagnosis of PD. One study found that 21 of 29 patients with PD had Lewy body pathology in colon tissue biopsied during the course of colonoscopy.[32]

Biological Biomarkers

Several different biomarkers in biological fluid—in the cerebrospinal fluid (CSF) as well as in the blood and urine—have been proposed for use in the diagnosis of PD. Challenges to the use of biomarkers revolve around the fact that fluctuations over the course of the disease can affect their measurable levels, and even their presence. Moreover, the manifestations of biomarkers in other neurocognitive diseases may be too similar to those seen in PD to allow them to be easily distinguishable.[33] It is reasonably likely that a combination of biomarkers will be required to achieve reliable early PD diagnosis.

Relative deposition of amyloid-ß, total-tau (an axonal death marker), and phospho-tau have shown evidence of utility as potential biomarkers in early PD, as well as in Alzheimer's disease.[34-36] Goldknopf et al, using 2D-gel electrophoresis, demonstrated that a panel of 21 proteins, out of a total of 57 initially identified, achieved PD diagnosis with both a sensitivity and specificity of 93% (**Table 2**).[37] Han et al have also recently published results of a study showing that disease-specific autoantibody testing achieved a sensitivity of 93% and a specificity of 100% for PD diagnosis in a study population that included 29 subjects with PD and 40 healthy controls.[38]

Genetic Biomarkers

Recent research into genetic biomarkers for early PD have shown promise and represent one of the most likely avenues

Table 2. Protein Biomarkers Allowing for Discrimination of PD from Healthy Controls With High Levels of Specificity and Sensitivity[37]

Protein Biomarker	Protein Identity	Functional Group[a]
N5514 Alb mutant R218H-I	Chain A albumin mutant R218H protein	IV
N5123 HP-2A	Haptoglobin HP-2a protein	II
N5515 X1	X1 protein	V
N1416 Factor I	Complement factor I protein	III
N3314 Apo E3	Apolipoprotein E3 protein	I
N3307 TT "D"	Transthyretin "dimer" protein	I
N7007 NUP 188	Nucleoporin NUP 188 protein	I
N2407 HP-1c	Haptoglobin HP-1 protein	II
N2511 Alb PRO2441	Albumin protein PRO2044	IV
N6306 PDLaH	Acidic histone H2A protein (PD/LBD)	I
N2502 Apo A-IV	Apolipoprotein A-IV protein	I
N3007 TT HYPE	Transthyretin HYPE protein	I
N7304 C4bγ	Complement C4b gamma chain protein	III
N4420 Alb mutant R218H-II	Chain A albumin mutant R218H protein	IV
N8301 Fidgitin I	Fidgitin protein I	I
N6224 Igκ	Immunoglobulin kappa light chain protein	III
N4411 factor H/Hs	Complement factor H/Hs protein	III
N8301 Fidgitin II	Fidgitin protein II	I
N3417 Alb PRO2675	Albumin protein PRO2675 protein	IV
N4130 X2	X2 protein	V
N4402 HP-RP	Haptoglobin related protein	II

PD indicates Parkinson's disease; LBD, Lewy body dementia.
[a]Functional groups: I – cell degeneration biomarkers: amyloid, oxidative stress, apoptosis, deoxyribonucleic acid repair; II – haptoglobin proteins: oxidative stress; III – inflammatory proteins: innate and autoimmune; IV – albumin proteins: transport; V – unknown function.
Reprinted with permission from Goldknopf IL, Bryson JK, Strelets I, et al. *Biochemic Biophys Res Comm.* 2009; 389:321–327.

for a reliable means of detecting early disease.[39] Newly published data from a study by Molochnikov et al, in 62 early-stage PD subjects and 64 matched controls, demonstrated that a 5-gene panel had a sensitivity of 90% and specificity of 89% in distinguishing early PD from controls.[40] The study also examined a separate cohort of advanced PD patients and patients with Alzheimer's disease and found that the 5-gene panel had 100% specificity in distinguishing these conditions from early PD.[40]

Neuroimaging

Several approaches to neuroimaging have been explored that have demonstrated viability in the detection of PD, including single photon emission computed tomography (SPECT), sonography, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI).[41] PET and SPECT examine in vivo brain function via radiotracers, and have been used to investigate, among other systems, the dopaminergic pathway in PD.[41] SPECT is more accessible to clinicians than PET and less expensive. In early PD, SPECT has been used to demonstrate a decrease in dopamine active transport in patients with unilateral symptoms.[42]

A 2007 meta-analysis of SPECT for PD diagnosis found it to be a fairly accurate modality in its ability to distinguish early PD from normal controls, and PD from essential tremor and VP, though less effective at differentiating PD from atypical parkinsonian syndromes.[43] A 2008 study compared the predictive value of transcranial duplex sonography versus SPECT for undiagnosed parkinsonian syndromes and observed that presynaptic SPECT was more specific than sonography for clinical diagnosis, but that an abnormal sonography offered a high degree of positive predictive value in subjects with parkinsonism with nigrostriatal degeneration. Consequently, sonography might have a role as a screening tool prior to use of SPECT.[44] Parkinson patients, it should be noted, possess marked hyperechogenic (increased amplitude or density in the sonographic image) substantia nigra, whereas patients with PSP and MSA typically have normal echogenic substantia nigra.[45] A 37-month study published in 2011, by Berg et al, described the results of transcranial sonography in 1535 subjects 50 years and older. The study established that for patients who exhibited enlarged substantia nigra hyperechogenicity at baseline, the relative risk of developing PD within 3 years was 17.37 versus subjects without hyperechogenicity (95% CI; 3.71-81.34).[46] These results suggest a potential role for cranial sonography in combination with other modalities in identifying early PD.

Sophisticated MRI techniques for the detection of early PD have been applied in recent years with some success. An Italian study in 30 PD patients and 22 matched controls found that the use of 3 markers—R2* values in left or right substantia nigra, fractional anisotropy values in right substantia nigra, and mean diffusivity in putamen or caudate nucleus—achieved over 95% global accuracy in distinguishing PD subjects from controls.[47] A high degree of diagnostic differentiation between PD and controls was achieved by Du et al in an MRI study which combined R2* and MRI diffusion tensor imaging (DTI), via fractional anisotropy, to detect changes in the substantia nigra.[48] Rolheiser et al have also demonstrated that DTI is effective in distinguishing PD subjects from healthy controls based on differences in both the substantia nigra and anterior olfactory region.[49] Ibarretxe-Bilbao et al used DTI to reveal microstructural white matter reductions in the olfactory systems of early PD patients.[50] These results suggest a potential utility of combined DTI and olfactory testing to achieve early diagnosis in PD.

Conclusions

Early diagnosis and treatment of PD are paramount to reducing the risk of disease progression, limiting the effects of PD on QoL, and potentially lowering long-term treatment costs. In a disease with a high rate of misdiagnosis, improving rates of correct diagnosis is vital, and requires educating clinicians regarding proper diagnostic approaches, ensuring diagnosis is performed by those clinicians with appropriate skill sets, and availing clinicians of emerging techniques for early and accurate diagnosis. Recognition of premotor symptoms is one of the key areas of opportunity for early PD diagnosis, and optimal accuracy in diagnosis is likely to be achieved by a combination of premotor symptom detection and other early diagnostic techniques. Biomarkers—biologic and genetic—offer some of the most promise for reliable early PD diagnosis, while neuroimaging, particularly SPECT and sonography (perhaps in combination), also show enormous potential for high degrees of sensitivity and specificity in diagnosing early PD. Taken together, these data point to an emerging awareness that the current diagnostic criteria, and techniques, should be revisited in light of current knowledge of PD in order to optimize early detection. New diagnostic criteria for PD are definitely in our future.

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