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Parkinson's Disease Monitor & Commentary

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Practical Analysis on Today's Findings in Parkinson's Disease

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From the editor...

DAVID J. HOUGHTON, MD, MPH

Even when data are objective, multiple points of view may be useful for interpretation. In this issue, like most issues of *PD Monitor & Commentary*, our reviewers identify limitations or problems overlooked by the principal authors, demonstrating why context from independent experts is always helpful, including in the evaluation of well-conducted studies with clear conclusions.

For example, Dr. Alberto Espay of the University of Cincinnati, who reviews a study that suggests autoantibodies will soon be employed in the early diagnosis of PD, identifies significant hurdles. Similarly, Dr. Michael Okun of the University of Florida suggests that extradural motor cortex stimulation for the treatment of PD may be further away than that implied by the authors of a study of this technique. Likewise, Dr. Lisa Shulman of the University of Maryland would like more studies to identify risk factors for nonmotor symptoms, and she expresses fundamental reservations about the design of a study that has attempted to do so.

In some cases, our experts endorse or are encouraged by specific study findings even when their reservations are significant. For example, Dr. William Ondo of the University of Texas Health Science Center in Houston likes the potential for caffeine to address PD-associated daytime somnolence even if he has reservations about the evidence so far. Dr. Daniel Kremens of Thomas Jefferson University, although cautious about data from a single study, is intrigued by evidence that the MAO-B inhibitor rasagiline may improve mood independent of motor effects. And, Dr. Georgia Lea of the Ochsner Clinic reports that a simple test to confirm clinically significant impulsivity in patients with PD may have immediate clinical utility even if more studies are needed to substantiate its value.

In the Q&A section, Colleen Knoop, MSN, APRN, with whom I used to work at the University of Louisville, explores the roles of nonphysician practitioners in managing Parkinson's disease (PD). Finally, in the controversy section, Dr. Kurt Jellinger and I take opposing sides on the issue of the utility of the Braak staging system in explaining the pathological progression of PD.

This issue of *PD Monitor* is particularly rich in practical issues in the management of PD, and we hope you find our commentaries elucidating. Suggestions for future issues are welcome. Please feel free to reach me at info@delmedgroup.com.

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PD Monitor & Commentary

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Faculty Disclosures

Dr. Alberto J. Espay has consulted for Chelsea Therapeutics and served on Advisory Boards for Abbott, Chelsea Therapeutics, Eli Lilly, Impax, Merz, Solstice Neurosciences, and Teva Neuroscience. He has received honoraria from Novartis.

Dr. David J. Houghton has served on a Speakers' Bureau for Teva Neuroscience.

Dr. Daniel E. Kremens has consulted for GE Healthcare, Merz, and Teva Neuroscience, and has served on Speakers' Bureaus for Allergan, Merz, Novartis, and Teva Neuroscience.

Dr. Georgia S. Lea has consulted for Teva Neuroscience.

Dr. William G. Ondo has served on Speakers' Bureaus for Allergan, GlaxoSmithKline, Ipsen, Lundbeck, Merz, and Teva Neuroscience.

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In This Issue

Commentaries

Q&A with Colleen D. Knoop, MSN, APRN

Controversies in PD

Decision making, impulsivity, and addictions: Do Parkinson's disease patients jump to conclusions?

First Author and Institution:
Atbin Djamshidian, MD, Reta Lila Weston Institute for Neurological Studies, University of London, London, United Kingdom.

Citation:
Movement Disorders. 2012;27:1137-1145.

Objective:
Evaluate whether patients with Parkinson's disease (PD) have elevated rates of impulsive behavior.

Type of Study:
Controlled, prospective study.

Result:
Using a beads task that assesses how much information individuals gather before reaching a decision, patients with PD and impulsivity could be differentiated from those without.

Conclusion:
The beads test is an effective tool for identifying impulsivity in patients with PD even in the absence of overt symptoms. Identification of impulsivity may be relevant to treatment choices.

According to published reports, about 14% of patients with PD placed on dopamine receptor agonist (DRA) therapy develop impulsive-compulsive behaviors (ICB), such as gambling, binge eating, or excessive shopping. Although some risk factors for ICB have been identified, such as young age at onset of PD, male gender, and family history of substance abuse, the reason why some patients develop this condition in response to DRA therapy and some do not is unknown. A tool to screen patients with PD on DRA for early signs of ICB is potentially useful because of the opportunity it can afford to modify management.

In this study, a beads task, which has been previously shown to detect impulsivity by evaluating how much information is gathered before a decision, was administered to 26 patients with PD and ICB, 27 patients with PD and without ICB, 36 individuals diagnosed with impulsive or compulsive behaviors, and 36 healthy controls. All were also tested with other cognitive measurements, including the Mini-Mental State Examination (MMSE).

Compared to healthy controls, all PD subjects, whether or not they had been diagnosed with ICB, made more impulsive and irrational choices in the beads task. Overall, patients without ICB made choices more similar to those with a history of compulsive gambling while those with ICB made choices more similar to those with a history of illicit drug use. There was no difference between PD groups in working memory. The beads task was calculated to have a positive predictive value of 96% and a negative predictive value of 92.3% for identifying patients with PD and ICB.

Relative to healthy controls, patients with PD have greater rates of impulsivity and compulsivity even in the absence of ICB. Although susceptibility to ICB is likely to be multifactorial, the beads task test appears to be an effective screening tool.

Commentary:

Georgia S. Lea, MD
Department of Neurology
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New Orleans, Louisiana

This was a well-designed and intriguing study. The data presented here suggest the beads task is a relatively simple but sensitive method of screening for ICB. This could be particularly useful in those patients when ICB is suspected but no overt or definite symptoms are reported by the patient or family members. Objective evidence of ICB could affect treatment decisions. In particular, one might be less likely to increase the dose of DRAs to control motor symptoms when considering therapeutic options.

This study had a relatively small sample size, so it would be useful to have these findings substantiated in a larger study involving more centers. However, I was impressed by the results and would be willing to consider this screening tool in selected patients. ICB only develops in a subset of patients, but it can be a meaningful clinical issue for both patients and family. To the degree that the beads task could identify cases of ICB when symptoms remain subtle, clinicians may have the opportunity to alter treatment strategies to avoid the problems associated with this complication before they become clinically meaningful. ■

Diagnosis of Parkinson's disease based on disease-specific autoantibody profiles in human sera.

First Author and Institution:
Min Han, MD, University of Medicine and Dentistry of New Jersey, Stratford, New Jersey.

Citation:
PLoS One. 2012;7:e32383.

Objective:
Identify sera autoantibodies diagnostic of Parkinson's disease (PD).

Type of Study:
Microarray analyses of human sera from subjects with PD and controls.

Result:
Ten autoantibodies were identified that provided a high rate of discrimination (sensitivity 93.1% and specificity 100%) between sera from patients with PD relative to controls.

Conclusion:
Protein microarrays provide a relatively simple, broadly available, and low-cost diagnostic method for PD that could have wide applications, including for presymptomatic PD diagnosis.

The diagnosis of PD is currently based on physical and neurological evaluations combined with the patient's history. A simple diagnostic test such as an assay of a biomarker has tremendous potential to improve care of PD, particularly by allowing the disease to be detected and treated at its early stages. Among potential biomarkers, autoantibodies may be relatively easy to isolate if those specific to PD could be identified.

In this study, sera samples from 29 patients with PD, 50 patients with Alzheimer's disease (AD), and 40 controls were subjected to microarray analysis along with sera samples from 30 patients with breast cancer and 10 patients with multiple sclerosis (MS). From a sample of serum autoantibodies that were expressed differently in patients with PD relative to controls, 10 were considered useful as a diagnostic PD signature.

When these 10 autoantibodies were employed to differentiate sera provided by patients with PD from sera provided by controls or those with other diseases, the sensitivity was 93.1% and the specificity was 100%. The authors conclude that this collection of biomarkers may provide a highly accurate, specific method of diagnosing PD.

If confirmed by others, an autoantibody test may have important clinical applications, particularly for early diagnosis of PD or for use in treatment trials.

Commentary:

Alberto J. Espay, MD
Director of Clinical Research
Department of Neurology
University of Cincinnati
Cincinnati, Ohio

Han and colleagues suggest that the urgent need for specific biomarkers in PD may come to a happy ending through the measurement of autoantibodies, given the impressive sensitivity and specificity reported. Many caveats temper our enthusiasm. Besides the lack of pathologic diagnosis and, therefore, a true gold standard against which to measure sensitivity and specificity, the autoantibody profile was compared with specimens of non-neurological (breast cancer) and non-primary neurodegenerative diseases (multiple sclerosis) populations. This is a diversion for a disease whose main challenges are its distinction from atypical parkinsonisms, such as multiple system atrophy (MSA), and its recognition at a very early, ideally premotor state.

Since the study cohort included 29 samples from "early, progressive [sic], and end-stage" PD (no further phenotypic information is given), it remains unclear whether the autoantibody profile can be replicated in very-early PD populations, whether it changes with greater disease severity, and, more importantly, whether it can reliably be identified among those with premotor and even preclinical PD.

Before opening the immunology door to the elusive biomarker kingdom, other groups will need to confirm these findings and determine the extent to which this autoantibody profile is of pathogenic relevance (in which case the profile should shed light on the underlying pathophysiology of PD), or an epiphenomenon of the disease (in which case the same profile will manifest in other disorders of α-synuclein aggregation, such as MSA and dementia with Lewy bodies). Although we shall wait for critical, better-guided replication efforts, I suspect these autoantibodies are far from becoming signatures of a PD-specific autoimmune response, let alone reaching biomarker potential. ■

Combined beneficial effect of rasagiline on motor function and depression in de novo PD.

First Author and Institution:
Alexei Korchounov, MD, Marienhospital Kevelaer, Kevelaer, Germany.

Citation:
Clinical Neuropharmacology. 2012;35:121-124.

Objective:
Evaluate prokinetic and antidepressive effects of rasagiline in patients with Parkinson's disease (PD).

Type of Study:
Prospective, randomized study of two rasagiline doses with blinded assessments.

Result:
While both the 1-mg and 2-mg doses of rasagiline improved motor function, the higher dose significantly reduced symptoms of depression not considered to be related to motor function.

Conclusion:
The 2-mg daily dose of rasagiline appears to have a direct antidepressive effect that is not dependent on relief of the motor symptoms that characterize PD.

Depression is common among patients with early, untreated PD. Although the pathophysiological relationship between motor symptoms and depression in early PD is unknown, there is evidence that those with depression have a more rapid cognitive and functional decline. Specific strategies to control depression in early PD have immediate implications for improving quality of life and may also affect prognosis.

In this study, 22 patients with newly diagnosed idiopathic PD with comorbid and untreated depression were randomized to receive 1 mg or 2 mg of daily rasagiline; six met the study criteria and were analyzed. Three assessments (Part 2 of the Unified Parkinson's Disease Rating Scale [UPDRS], which assesses activities of daily living; Part 3 of the UPDRS, which assesses motor function; and the Hamilton Depression Rating Scale [HDRS]) conducted at baseline were repeated after 8 weeks by investigators blinded to the assigned therapy.

At the end of the 8-week treatment period, there were improvements in motor symptoms from baseline in both groups. The authors did note that there was slightly more improvement in bradykinesia and rigidity relative to tremor, but this effect did not differ by dose. However, there were significant between-group differences in both the HDRS and the activities of daily living score favoring the higher dose. On the HDRS, the advantage was consistent across core symptoms of depression. Importantly, the authors note that improvement was seen in symptoms not considered movement related, including mood, guilt, and psychic anxiety.

The greater antidepressive effect associated with the higher dose of rasagiline did not appear to derive from a change in motor symptoms but rather from an independent effect on mood.

Commentary:

Daniel E. Kremens, MD, JD
Parkinson's Disease and Movement Disorders Center
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This is an interesting paper with a result that certainly warrants additional studies. Demonstrating an independent benefit on adverse changes in mood among patients with PD would be a valuable clinical effect. However, this study has to be considered very preliminary and interpreted with caution because it was small and it did not include a control arm. In addition, the 8-week study period was relatively short; previous studies have demonstrated improvements in motor function on rasagiline for up to 12 weeks.

The conclusion from these data that rasagiline may have independent favorable effects on depression was reasonable based on the analysis, but due to the small sample size and lack of a control arm, this should be considered hypothesis generating. A blinded study conducted over a longer period is now needed to further explore this potential effect. The importance of a blinded study, particularly one conducted with an active control, is that quality of life improves on any effective antiparkinsonian therapy, which might have an impact on mood even for symptoms of depression not normally related to movement symptoms. Nevertheless, it is plausible that an MAO-B inhibitor could have favorable effects on mood, and this research encourages additional studies. ■

Prevalence of nonmotor symptoms in young-onset versus late-onset Parkinson's disease.

First Author and Institution:
Vladana Špica, MD, University of Belgrade, Belgrade, Serbia.

Citation:
*Journal of Neurology.*2012;Epub ahead of print.

Objective:
Identify the relative risk of nonmotor symptoms (NMS) in young- versus late-onset Parkinson's disease (PD).

Type of Study:
Prospectively administered questionnaire.

Result:
Contrary to expectation, the prevalence of NMS was lower in young-onset than late-onset patients with PD although a broad array of such symptoms was observed in both.

Conclusion:
Awareness of the differences in predominant NMS in young- versus late-onset PD may be useful in managing and understanding these phenotypes.

There has been an increasing appreciation for the presence and impact of NMS in patients with PD. Cognitive disturbances, mood changes, urinary and sexual function, and loss of taste are among a long list of NMS that may impose a significant reduction in quality of life. Some but not all may occur independent of changes in dopaminergic function. While several differences in young- and late-onset PD have been proposed, the relative risk of NMS has not been well defined.

In this study, a validated comprehensive questionnaire designed to elicit information about the presence and severity of NMS was administered to 101 patients with young-onset PD (diagnosis between age 21 and 45 years) and 107 with late-onset PD (diagnosis at age 55 year or older). The data were assessed to compare the mean total of NMS as well as capture differences in the predominant NMS.

The mean number of NMS was greater in those with late- than young-onset PD (11.9 vs. 7.7; $P<0.05$). The only NMS more prevalent in young-onset PD were restless legs and sweating. The NMS more common in late-onset PD included dribbling of saliva, loss of taste or smell (or both), nocturia, cognitive symptoms such as forgetfulness, hallucinations, and mood disorders, such as anxiety and loss of interest in daily activities. However, of nine domains, the three most prevalent in both young- and late-onset PD were depression/anxiety, urinary function, and sexual function.

There were some potential confounders, such as a higher average levodopa dose in the younger patients, but these differences were not considered of sufficient magnitude to alter the conclusion that older PD patients experience more NMS. It is notable that despite similar PD severity, the young-onset patients rated their quality of life lower even though they had fewer NMS.

Commentary:

Lisa M. Shulman, MD
Professor of Neurology
University of Maryland School of Medicine
Baltimore, Maryland

Understanding the relative risk of NMS in young-onset versus older-onset PD is potentially important for guiding patient management. However, this study had limitations. First, comorbidities were not measured. This is an important potential flaw because many of the nonmotor symptoms that they compared between the age groups, such as nocturia, cognitive dysfunction, and sexual dysfunction, may be related to medical problems other than PD. If, as one would anticipate, comorbidities are more common in an older population, this may explain why these investigators found a higher rate of nonmotor symptoms in an older population.

Understanding the relative risk of NMS in young-onset versus older-onset PD is potentially important for guiding patient management.

Another potential confounder in this study was the longer duration of PD in younger versus older patients. This may simply reflect a delay in the diagnosis in the older patients, a common phenomenon because early signs of PD mimic the physical signs of aging. If there are important differences in the relative risk of NMS by age or any other discriminator, this could be helpful for raising the index of suspicion when evaluating patients. This is an intriguing concept, but the problems with this study challenge the authors' conclusions. ■

Unilateral extradural motor cortex stimulation is safe and improves Parkinson's disease at 1 year.

First Author and Institution:
Anna Rita Bentivoglio, MD, Catholic University, Rome, Italy.

Citation:
*Neurosurgery.*2012;Epub ahead of print.

Objective:
Test safety and efficacy of unilateral extradural motor cortex stimulation (EMCS) over 1 year in patients with Parkinson's disease (PD).

Type of Study:
Single-center, uncontrolled study.

Result:
Off medication, the stimulation was associated with substantial reductions in active symptoms relative to baseline at 1, 3, 6, and 12 months with a corresponding improvement in quality of life.

Conclusion:
Unilateral EMCS was found to be safe and to provide a modest but significant improvement in symptoms that encourages larger studies.

In patients with PD who are poor candidates for deep brain stimulation (DBS) due to frail health or other reasons, less invasive techniques have been sought. There is some clinical experience and several theoretical reasons to propose EMCS as a potential alternative strategy, but there are few prospectively planned studies that include extended follow up.

In this study, 11 patients were selected for EMCS based on several criteria, including unsatisfactory management of fluctuations with drugs and lack of eligibility for DBS. All demonstrated at least a 33% reduction in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score with dopaminergic therapy. All had quadripolar electrode strips implanted over the motor cortex. Stimulation was delivered continuously. Nine patients were followed for at least 12 months.

When assessed under the off-medication condition, the UPDRS III scores relative to baseline were reduced on average by 14.1% at 1 month, 23.3% at 3 months, 19.9% at 6 months, and 13.2% at 12 months. The UPDRS IV scores were reduced on average at these timepoints by 40.8%, 42.1%, and 35.5%, at 1, 3, and 12 months, respectively. In one patient whose device was unintentionally switched off, the effects appeared to persist for up to 4 weeks. A persistent improvement in quality of life (QOL) from baseline was documented with a PD QOL questionnaire. There were no complications for implantation, and no side effects, including no loss of cognitive function, were reported.

The authors characterize EMCS as safe and modestly effective. Although they call for further studies, they conclude that EMCS may be an important therapeutic option for patients with PD and prominent axial symptoms, severe dyskinesias, and relative contraindications to DBS.

Commentary:

Michael S. Okun, MD
Co-Director, Center for Movement Disorders and Neurorestoration
University of Florida
Gainesville, Florida

The potential advantage of unilateral EMCS is that it is implanted "upstream" in the basal ganglia circuitry, which offers a safety advantage over DBS. This therapy has a subdural electrode placement, which is less invasive than other published techniques. However, it is not clear whether this therapy works on neurons, oscillations, interneurons, or a complex neuronal network, and it may be necessary to treat more tissue with cortical stimulation than with DBS. Functional imaging and physiology studies have not yet identified a mechanism of action.

One issue with this paper is that the candidates seemed similar to those currently receiving DBS, yet the benefit was much less. The claim by the authors that axial symptoms responded best to this therapy was interesting, but this will require validation.

The field desperately needs better treatments for walking, talking, gait, and balance dysfunction in PD. The 13% improvement at 12 months in this open-label surgical trial was disappointing given the high placebo effect and the large potential for rater bias. Overall, published results should have no immediate relevance to patient care. More documentation of benefits (particularly axial benefits) and a lack of adverse events will be needed. ■

Caffeine for treatment of Parkinson's disease: A randomized, controlled trial.

First Author and Institution:
Ronald D. Postuma, MD, MSc, McGill University, Montreal, Canada.

Citation:
Neurology. 2012;79:651-658.

Objective:
Evaluate caffeine for treatment of somnolence in Parkinson's disease (PD).

Type of Study:
Randomized, placebo-controlled trial.

Result:
Caffeine did not produce a significant improvement in the primary endpoint of daytime somnolence, but was associated with an improvement in observed measures of motor function.

Conclusion:
Despite the lack of benefit on the primary endpoint, other objective benefits encourage a larger and longer multicenter study of the clinical utility of caffeine in PD management.

As a non-selective antagonist of adenosine receptors, caffeine has several characteristics that suggest it might be useful in the treatment of PD. Not least of these is that epidemiologic studies associate high levels of caffeine intake with protection from developing PD. As a treatment, caffeine is especially attractive for treating the excessive somnolence that is frequently associated with PD.

In this study, 61 patients were randomized to receive caffeine or matching placebo. The initial caffeine dose, administered for 3 weeks, was 100 mg twice daily. It was raised to 200 mg twice daily for the subsequent 3 weeks of this 6-week study. The primary endpoint was change in the Epworth Sleepiness Scale (ESS), but change in motor function, quality of life (QOL), and sleep markers were included as secondary endpoints.

The average 1.71 point reduction in the ESS score among patients randomized to caffeine relative to those given placebo did not reach statistical significance. However, the overall 4.69 reduction in the Unified Parkinson's Disease Rating Scale (UPDRS) score was significant, and there were favorable changes in several symptom subscales. There was no difference in the rate of adverse events in the caffeine and placebo arms.

The study did not confirm a significant benefit against PD-associated somnolence, but the improvement in motor measures led the authors to recommend a larger and longer study.

Commentary:

William G. Ondo, MD
Professor of Neurology
University of Texas Health Science Center
Houston, Texas

Excessive daytime sleepiness is a major problem in PD. It is a function of the disease itself and dopaminergic and other medications used to treat it. There is no established pharmacotherapy for the problem, although modafinil studies have shown mixed results.

In this trial, as expected, caffeine was well tolerated, without any meaningful side effects. The ESS score tended to improve, by 1.7 points, but this was not statistically significant. Clinical Global Impressions of sleepiness did statistically improve. The total UPDRS score modestly but significantly improved. This was largely powered by improvement in the motor examination, which was done while "on" other Parkinson medications. Other measures did not change.

Given the benign side-effect profile of caffeine, I think it is not unreasonable to consider its use in patients with excessive daytime sleepiness.

The study was technically negative in that it did not reach the primary efficacy point; however, secondary endpoints of sedation and the motor examination did significantly improve. While interpretation of motor examination while patients are "on" PD medications is always problematic, one rationale for anticipating improvement with caffeine is that other medications with similar mechanisms of action have shown motor benefit.

Given the benign side-effect profile of caffeine, I think it is not unreasonable to consider its use in patients with excessive daytime sleepiness. ■

Q&A

WITH
Colleen D. Knoop, MSN, APRN
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Question: What are the roles of nonphysician practitioners in managing Parkinson's disease (PD)?

Answer: Nurse practitioners (NPs) and physician assistants (PAs) are utilized in numerous movement disorder centers around the country. The roles of these nonphysician practitioners for the management of PD can be quite broad, but they should be based on the training, knowledge, and comfort level of the individual provider. It is important to note that state regulations may also drive how nonphysician practitioners are able to practice.

The nonphysician practitioner trained in the treatment of PD may feel quite comfortable managing the patient independently. I have some patients that I follow exclusively, but I will discuss that patient with a physician or have a physician see the patient when I have questions or concerns. Certainly, it is crucial that nonphysician providers recognize their personal limitations and seek guidance when necessary. In my setting, the majority of patients see both a physician and an NP/PA one to two times per year each. The frequency of visits to NPs/PAs are scheduled according to patient and provider preferences, but typically patients see the nonphysician providers more often than the physicians and often for follow-up and work-in appointments, since they may have more flexibility built into their clinic schedules than physicians. This can be very beneficial from a patient care/satisfaction perspective, and reduces the potential for double-booking physicians. Ultimately, the goal is to free the physician's follow-up schedule to allow for more new patient openings, thus generating more revenue for the practice.

It is my experience that this population of patients and families is highly motivated to seek information about PD throughout the disease course, not just at time of diagnosis. Nonphysician practitioners can play a very active and important role in educating and empowering patients and caregivers. This is generally accomplished during the follow-up visit. When a provider, physician or nonphysician, sees that more extensive education is needed, a follow-up, perhaps with additional time, can be scheduled with the NP/PA so that the primary focus of the visit can be spent on addressing specific questions or issues. As a nurse and NP, I received a great deal of training on the importance of patient education and caring for the patient holistically. Through the expanded and continued education NPs can offer patients and families, they gain additional perspective and expertise that complements the care received by the physician.

Nonphysician practitioners often play active roles in deep brain stimulation (DBS) programs. This may include patient selection, pre- and postoperative education, on/off testing, and intra-operative examinations, as well as postoperative programming and troubleshooting. In our program, the nonphysician practitioner plays an active role on the multidisciplinary DBS team. This assures that patients progress through the work-up phase efficiently, as well as offers an additional provider option so that patients can be eased into the schedule more easily and in a timely manner.

In regard to research, nonphysician providers can certainly play an important role on the research team, acting as subinvestigators or even carrying out their own research, or their role may be confined to understanding various open clinical trials so they can recruit potential participants.

In summary, there are many ways that nonphysician practitioners can be utilized in the management of PD as productive members of the team. Whether it is a physician or nonphysician practitioner, by our training and experience, we all have something meaningful to add toward the management of the patient with PD and his or her family.

Controversies in PD

PRO Opinion

David J. Houghton, MD, MPH
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Over the past 10 years, there has been much discussion in the PD community regarding the neuropathological staging system proposed by Braak.[1] This six-stage system follows the presumed spread of Lewy bodies (LBs) from the anterior olfactory nucleus and dorsal motor nucleus of the vagus nerve (stages 1 and 2), into the substantia nigra (SN, stages 3 & 4), and terminates in diffuse cortical disease (stages 5 and 6). Repeated efforts to validate this system have been largely successful, and a recent re-analysis of the Braak dataset demonstrated that only 9% of patients did not fit the staging schema.[2-4] The idea remains controversial, however, and other research has found disconcordance in up to 47%.[4]

The staging system relies on the presumption that pathologically evident LBs in Braak stages 1 and 2 occur in the absence of clinically evident idiopathic PD (iPD). Such incidental LBs and loss of neurons may account for the common premotor manifestions of iPD (e.g., hyposmia, REM behavioral disorder, constipation, mood disorders, and dysautonomia). As the pathology progresses rostrally to the SN, the common motor symptoms appear—often with worsening nonmotor features accounted for by advancing brainstem pathology. Evidence is growing in support of the "spreading" nature of many neurodegenerative diseases, particularly the proteinopathies.[5-6] This "prion-like" theory dovetails with the Braak staging model of PD. Although controversy exists regarding the direct pathological nature of misfolded alpha-synuclein (αSyn) and LBs, it remains the most reliable cellular fingerprint upon present neurons scattered among a growing absence.[7] Neurons with initial sites of damage in the anterior olfactory nucleus, as well as enteric neurons of the gut or dorsal motor nucleus of the caudal medulla, slowly continue their swath of damage in a rostral pattern up to the SN and beyond to the cortex.[1]

The primary criticism of the Braak staging system relates to the lack of concordance for some patients. As this requires the gold standard to be the clinical diagnosis, some inability of the Braak staging technique to explain all clinical cases of iPD may not be an indictment of this pathological system; rather, some cases of clinicopathological incongruence could arise from diagnostic uncertainty. As proposed by Weiner et al, we are actually diagnosing and treating "Parkinson's diseases" already—nearly as many combinations and permutations of tremor, slowness, stiffness, postural instability, freezing of gait, dyskinesia (chorea, dystonia, tics), dysautonomia, dysarthria, sleep dyscrasias, cognitive impairment, sensory disturbances, and mood changes as we have patients.[8] And all of these are wrapped in a history of potential genetic, environmental, and comorbid influences. To wit, given the myriad changes to the nervous system that accompany iPD over time, the nearly unifying Braak pathological system of progression seems quite remarkable.

I believe the basic decision of acceptance or rejection of the Braak hypothesis boils down to this: Do you reject based on the exception or do you accept based on the rule? I accept the rule, I accept there are exceptions, and I expect the exceptions are acceptable to most.

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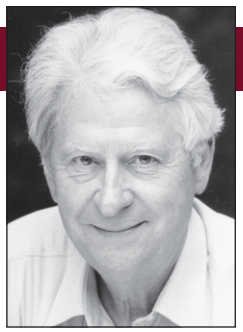
The Question: Does the Braak staging system adequately explain the pathological progression of Parkinson's disease (PD)?

CON Opinion



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The validity of the six-stage Braak system, which corresponds roughly to the classification of LB disorders, has been accepted by some, but has been the subject of vigorous debate, since between 6.3% and 47% of all cases of autopsy-proven PD and 18% of incidental LB disease do not follow caudo-rostral spread of Lewy pathology.[1-10] In 7%-8.3% of PD cases, the dorsal motor nucleus of vagus nerve (DMX) is not involved despite definite αSyn inclusions in the higher brainstem or even in cortical regions.[8,10,11] Furthermore, no relationship between LB stage and both clinical severity of PD (Hoehn & Yahr score) and age of death have been found.[7] Metabolic and functional abnormalities associated with prodromal parkinsonian changes already occur in the nervous system in early disease stages, not accompanied by Lewy pathology, while some early nonmotor symptoms may occur in patients with Braak stages 1 and 2.[8,12-16]

The duration and severity of motor dysfunction in PD, the corresponding decrease of the dopamine transporter (DAT), and vesicular monoamine transporter 2 (VMT2) immunoreactivity in the striatum are inversely correlated with the total αSyn burden and neuronal loss in the SN, but not with LB counts in the SN, which supports the concept of synaptic dysfunction and impairment of axon transport.[6,13,17-20] Recent studies suggest a dying-back mechanism in diseases with neuronal αSyn pathology, in which dysfunction starts at the synapse and leads to axonal degeneration and αSyn accumulation in LBs and dystrophic neurites.[21] These data and the demonstration of the accumulation of αSyn aggregates at presynaptic terminals in PD and dementia with LB (DLB) suggest that related synaptic dysfunction or axonal degeneration, not nerve cell loss, may be the primary determinant of progression of neurodegeneration.[22] LBs are considered markers of ongoing neuronal damage, or might even be harmless end products of sequestration of toxic molecules as a type of cell-protective mechanism.[6] Unfortunately, the Braak staging of Lewy pathology does not consider αSyn, the biochemical increase of which precedes αSyn aggregation, followed by formation of LBs and dystrophic neurites.[23]

According to the Braak staging system, 49%-50% of elderly individuals with widespread αSyn pathology lack clinical symptoms or are nonclassifiable. A recently proposed unifying system for LB diseases, distinguishing four stages, showed significant correlations between αSyn pathology with striatonigral degeneration, reduction of striatal tyrosin hydroxylase, SN cell loss, and clinical scores.[10,11,24] Use of this system allowed correct classification of all cases with LB diseases. If validated in further clinicopathological studies, this new staging system would improve on its predecessor by allowing classification of a greater proportion of patients.

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