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Parkinson's Disease Monitor & Commentary

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

From the editor...

ANDREW D. SIDEROWF, MD

In this, our final issue for 2009, we have again assembled an eclectic group of articles that reflect the diversity of research in Parkinson's disease (PD). These range from a study of optogenetics that has the potential to provide breakthrough information for improving deep brain stimulation, according to our review from Dr. Jay Shils of the Lahey Clinic in Massachusetts, to a review of a clinical trial that tested disease modification with a monoamine oxidase type-B inhibitor. This latter study, published in the *New England Journal of Medicine* and evaluated by Dr. Lawrence Elmer, of the University of Toledo (and one of the investigators on the study), tackles the thorny issue of just how disease modification in PD should be defined.

Several of the studies in this issue suggest incremental but important steps in areas that have enormous potential to alter perceptions of PD. In his review of a study with positron-emission tomography (PET) to track brain alterations in acetylcholinesterase among patients with PD and dementia, Dr. Andrew Feigin of the Feinstein Institute of Medical Research in Manhassett, New York, acknowledges that the study adds to growing appreciation that neurotransmitters other than dopamine are important in PD pathology. These kinds of advances are critical to addressing a set of symptoms much broader than dyskinesias.

For those who wish to keep track of how basic science makes the leap to feasible new approaches in the clinic, Dr. Claire Henchcliffe of Cornell's Weill Medical College reviews a study claiming to have produced the best animal model yet in regard to mimicking clinical features of PD. Whether or not this model will fulfill its promise, the characteristics allow Dr. Henchcliffe to provide some insight on exactly what type of model is needed to translate advances in basic science to clinical application.

Our mix of studies is intentional. This is a publication that is designed to provide practicing neurologists with insight into some of the current areas of research. Our reviewers are specifically enlisted to evaluate studies in areas where they themselves are active researchers or which they have been following closely. For those who find a topic interesting, we always recommend the original source. If you have comments or suggestions, please feel free to reach me at info@delmedgroup.com.

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In This Issue:

PD Monitor & Commentary

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Treatment disparities in Parkinson's disease.

First Author and Institution:
Nabila Dahodwala, MD, University of Pennsylvania, Philadelphia.

Citation:
Annals of Neurology. 2009;66:142-145.

Objective:
Evaluate racial disparities in the treatment of Parkinson's disease (PD).

Type of Study:
Retrospective review of Pennsylvania Medicaid claims for treatment.

Result:
African-Americans were four times less likely to receive treatment for PD than Caucasian patients after controlling for age, sex, and geography.

Conclusion:
The reduced likelihood that African-Americans will receive treatment for PD encourages studies to uncover the causes, which appear likely to be multifactorial (including patient- and physician-related).

In PD, delays in initiating disease-modifying agents have been associated with accelerated disease progression. In African-Americans, previous studies suggest that lack of appropriate care leads to increased morbidity and diminished quality of life.

In this study, 307 incident PD cases were examined from the Medicaid database in the state of Pennsylvania. Of the sample, 14% of patients were African-American and 86% were white. Women represented 61% of the study population. The mean age at diagnosis was 55 years.

African-Americans were less likely to be prescribed medication or physical therapy (12% versus 38%; P=0.002) and less likely to receive just drug treatment (12% vs. 33%; P=0.008). When multivariate odds ratios for receiving treatment were calculated for African-Americans versus Caucasians regarding age, gender, care setting, physician specialty, and Medicaid eligibility, only race and age were significantly associated with any medication treatment or physical therapy, with treatment odds ratios of 0.24 (95% CI 0.09-0.64) and 1.67 (95% CI 1.02-2.73), respectively.

This type of analysis did not permit the authors to evaluate clinical status, such as severity, or the presence of co-morbid conditions, which may have affected the decision to treat.

Commentary:

Eric Cheng, MD, MS
Assistant Professor of Neurology
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Disparities of health and health care by race have been observed for many conditions. Using administrative data from a state Medicaid program, this study detected racial disparities for a specific process of care—use of PD medications or physical therapy—among persons with newly diagnosed PD. Although not measured, such differences in care could eventually lead to differences in symptom amelioration and overall health outcomes among persons in this cohort.

The main advantage of using administrative data is the ability to analyze a large sample. Given the size of the cohort and the considerable absolute difference in treatment rates, it is highly unlikely that the well-known limitations of using administrative data—misclassification using diagnosis codes, incomplete data capture, unavailable clinical variables—would fully account for this gap.

Studies of depression and influenza vaccination have shown that minority patients are less likely to accept certain forms of treatment even when they are equally likely to be offered because of perceived lack of efficacy or concern about adverse effects. Practicing clinicians should be aware that providing a clear and accurate description of the benefits and risks of treatment is important when treating all patients, but especially so among minority patients. ■

A double-blind, delayed-start trial of rasagiline in Parkinson's disease.

First Author and Institution:
C. Warren Olanow, MD, Mount Sinai School of Medicine, New York, New York.

Citation:
New England Journal of Medicine. 2009;361:1268-1278.

Objective:
Evaluate the disease-modifying effects of rasagiline in Parkinson's disease (PD).

Type of Study:
Double-blind, multicenter, randomized trial.

Result:
All three predefined end points were met with the 1-mg dose of rasagiline but not the 2-mg dose.

Conclusion:
There is a possible disease-modifying effect from early use of rasagiline at 1 mg per day, but the authors withheld a definitive conclusion for further follow-up because of the lack of the same benefit from the 2-mg dose.

Although several drugs, including rasagiline, have been demonstrated to have disease-modifying activity in the laboratory, no drug has demonstrated such activity clinically. One obstacle has been controversy about which end points prove disease-modifying activity.

In this study, 1,176 patients with untreated early PD were randomly assigned to early or delayed treatment, a trial design developed to look for disease-modifying effects. In the early-start group, patients were further randomized to 1 mg rasagiline per day, 2 mg rasagiline per day, or placebo for 72 weeks. In the delayed-start group, all patients received placebo for the first 36 weeks and then were randomized to rasagiline 1 mg or 2 mg per day for the subsequent 36 weeks. The effect of early treatment on disease-modifying activity was judged with three hierarchal end points based on the Unified PD Rating Scale (UPDRS): superiority to placebo in rate of change at 36 weeks, superiority to delayed start at week 72, and non-inferiority for rate of change in the early- versus delayed-start groups between weeks 48 and 72.

The early-start 1-mg dose met all three end points (P=0.01, P=0.02, and P<0.001, respectively). The early-start 2-mg dose was superior for two of the end points (both P<0.001), but was not significantly better than the delayed-start 2-mg dose for UPDRS score at 72 weeks (P=0.60).

The trial design required significant advantage over placebo and delayed therapy for all three end points in order to report disease-modifying activity. Even though the 1-mg dose did show this advantage, the lack of statistical benefit on one of the end points with the 2-mg dose required the authors to conclude that definitive proof of disease-modifying activity had not been shown, although they found it difficult to explain why the two doses did not show similar results.

Commentary:

Lawrence Elmer, MD, PhD
Medical Director, Center for Neurological Health
Professor of Neurology
University of Toledo Medical Center
Toledo, Ohio

In part due to the controversy that will be generated by the design and results of this trial, the NEJM *published supplementary material with several post hoc analyses with this paper. These data show that the 2-mg dose was highly effective for all three end points in the quartile of patients with the highest UPDRS scores at baseline (>25.5). For those in the lower quartiles, the delayed 2-mg dose appeared to provide such a robust reduction in symptoms that it was difficult for the early-start therapy to show a relative advantage at 72 weeks. Although the same pattern was observed with the 1-mg dose, the overall advantage in the highest UPDRS quartile was sufficient to confer statistical significance overall.*

This study does suggest disease-modifying activity, but the FDA does not permit post hoc analyses to be employed for labeling and indication purposes. Another study may be required to prove that rasagiline alters the natural history of patients with moderate symptoms rather than the earliest symptoms of PD.

The message to clinicians is that there are symptomatic benefits of early therapy using rasagiline, a compound with a side effect profile similar to placebo, and there is now at least a suggestion of disease-modifying activity. ■

Editor's note: Dr. Elmer was one of the investigators in this trial.

Occupation and risk of parkinsonism.

First Author and Institution:
Caroline M. Tanner, MD, PhD, The Parkinson's Institute, Sunnyvale, California.

Citation:
Archives of Neurology. 2009;66:1106-11113.

Objective:
Evaluate the relationship of occupations to risk of parkinsonism.

Type of Study:
Multicenter, case-control study.

Result:
Occupational exposure to pesticides was the most consistent risk factor for parkinsonism, but no specific occupation remained a risk factor for parkinsonism after adjustment for duration.

Conclusion:
The strong association of specific pesticides with the development of parkinsonism supports the likelihood of a chemically induced disease process in at least some individuals.

Case-control studies have implicated several occupations, including those in agriculture, education, and health care, with an increased risk of developing Parkinson's disease (PD). It is presumed that these associations derive from exposure to specific neurotoxic chemicals. Some toxicants, including pesticides, have been implicated.

In this case-control study, 519 patients with PD and 511 controls matched by age, sex, and location were compared for life-long occupational and job-task exposures. The median baseline characteristics, including gender (59% male), age (65 years), race (predominantly Caucasian), and years of education (16) were the same in the study and control groups.

There were unexpected increases in PD among legal, construction/extraction, and religious occupations, but these did not persist after risk was adjusted for duration of exposure. After adjustment, no occupation, including welding/machining (which has previously been implicated as a risk factor for PD), remained significantly associated with an increased risk of PD. However, occupational use of pesticides—most significantly the organochlorine 2,4-dichlorophenoxyacetic acid, the herbicide paraquat, and the insecticide/acaricide permethrin, all of which have effects on dopaminergic neurons in experimental settings—was independently associated with an almost 80% greater risk of developing PD. People who had ever smoked tobacco had an inverse risk of PD.

The findings support previous evidence that exposure to pesticides may contribute to the risk of developing PD.

Commentary:

Michael Schwarzschild, MD, PhD
Director, Molecular Neurobiology Laboratory
Massachusetts General Hospital
Associate Professor of Neurology
Harvard Medical School
Boston, Massachusetts

This study incrementally adds to our understanding of how environmental factors may influence the risk of developing PD and related disorders. It further strengthens the link to pesticide toxicants, including several that had been previously suspected based on laboratory as well as prior epidemiological studies. These are helpful steps, because the strongest prospective data that has previously associated PD risk to pesticide exposure gave few clues as to which pesticides might pose the greatest risk. This study identified several pesticides of interest, including an organochlorine that has not been prominently linked to PD until this study.

These findings do not prove causality, but they are useful for refining efforts to identify where to focus research on the role of environmental factors. This study also reduces concern about the risk posed by some professions, such as welding, that had been implicated as possible risk factors for PD.

Although case-control studies have inherent potential biases, this study was of a reasonable size with well-matched subjects and controls. On the basis of these findings, it is reasonable to encourage individuals to take standard but often neglected precautions in handling pesticides whether as an occupational exposure or in weekend gardening. Pesticide labels should be read and instructions followed carefully. Appropriate protective equipment and clothing include a mask or respirator that reduces inhalation and gloves to reduce skin and oral exposure. Though we have no definitive evidence that these protective measures will reduce the risk of developing PD or reduce the risk of progression in those who already have PD, they are prudent steps based on the information now available. ■

Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET.

First Author and Institution:
H. Shimada, MD, Institute of Radiological Sciences, Chiba, Japan.

Citation:
Neurology. 2009;73:273-278.

Objective:
Characterize brain cholinergic deficits in Parkinson's disease (PD) and Lewy body dementia.

Type of Study:
Prospective study employing positron emission tomography (PET).

Result:
Cholinergic dysfunction occurs in the cerebral cortex and increases in the presence of dementia.

Conclusion:
Cholinergic denervation is common in the cortex of patients with PD, does not parallel dopaminergic denervation, and may be an important mechanism of dementia.

Although dopaminergic impairment is most closely associated with the movement symptoms of PD, dysfunction of other neurotransmitter systems is suspected in playing a role in PD expression. Efforts to quantify brain cholinergic function by measuring acetylcholinesterase (AChE) activity in patients with PD relative to dementia has substantial potential to help determine its role in the cognitive decline that frequently accompanies this disease.

In this study, brain AChE activity was measured with PET scanning in 18 patients with PD, 21 patients with PD and dementia or Lewy bodies and dementia, and 26 healthy controls. Cortical values were measured in the frontal, temporal, parietal, and occipital cortices in both hemispheres. Values were evaluated in the context of Mini-Mental Status Examination (MME) scores and duration of PD.

Relative to controls, AChE activity was significantly reduced by 11.8% in the cerebral cortex of all patients with PD, and by 26.8% in those with PD with dementia or Lewy body dementia ($P<0.01$). When the PD group without dementia was compared to the combined dementia groups, there were greater reductions in AChE activity in the dementia groups. The relative decline was particularly pronounced in the supramarginal gyrus ($P<0.005$) and the posterior cingulate gyrus ($P<0.01$).

The authors emphasized that even some newly diagnosed patients had reductions in AChE activity, suggesting that brain cholinergic dysfunction occurs early in the course of PD, and that there did not seem to be a progressive reduction in AChE activity with duration of PD. The fact that the reduction in AChE activity was more pronounced in the groups with dementia relative to those without dementia is consistent with the premise that impaired AChE activity is a mediator of cognitive loss in patients with PD.

Commentary:

Andrew S. Feigin, MD
Head, Laboratory of Experimental Therapeutics
Feinstein Institute for Medical Research
North Shore-Long Island Jewish Health System
Manhasset, New York

Non-motor, non-dopaminergic brain systems have long been known to be affected in PD, but this study, which employed PET imaging to evaluate brain alterations in AChE, adds additional support. However, there are some caveats to consider. Although the authors claim an association even in mild disease based on a cross-sectional analysis, about half of patients with mild disease actually demonstrated normal cholinergic activity. This raises the possibility that cholinergic dysfunction may not be present in all patients with PD but may be limited to specific subgroups. In addition, the diagnostic groups in the study (PD, PD with dementia, and Lewy body disease with dementia) were based on a clinical diagnosis, which we know has limited reliability; specifically, it is possible that at least some patients in this study had Alzheimer's pathology as well as PD.

It would be useful to have a long-term prospective study using imaging to see how patients evolve over time to better understand how changes in brain cholinergic function contribute to symptom expression in PD. Nonetheless, given that cholinesterase inhibitors have been found to improve cognitive function in patients with PD, this study lends further support to the idea that the cholinergic system may be a suitable target for improving cognitive function in PD. ■

Optical deconstruction of parkinsonian neural circuitry.

First Author and Institution:
Viviana Gradinaru, MD, Stanford University, Stanford, California.

Citation:
Science. 2009;324:354-359.

Objective:
Identify distinct neural circuits within a rodent model of Parkinson's disease (PD) to guide placement of deep brain stimulation (DBS) electrodes.

Type of Study:
Experimental study in animal model.

Result:
Frequency-dependent effects on afferents in the subthalamic nucleus correlated with symptom control, implicating targetable circuits for DBS.

Conclusion:
A methodology for isolating targetable circuits promises greater precision and greater benefit from DBS in PD and other neurological disorders.

The depletion of dopamine neurons in the basal ganglia and the altered activity of the subthalamic nucleus and globus pallidus pars interna are thought to be key events in the expression of the impaired movement that characterizes PD. Although high-frequency DBS has demonstrated efficacy in controlling symptoms in medically refractory PD, the mechanisms of action and the optimal targets of DBS have been unclear. One obstacle has been the inability to directly track how DBS affects neural circuits.

In this series of studies, the authors employed optogenetics, a technique they developed that employs fiber optics to detect firing action potentials *in vivo*. The genetically targeted photosensitization of circuit components within the subthalamic nucleus is coupled with optical control and electrophysiological recording. Activity can be measured within specific cell types at the time of stimulation, allowing real-time monitoring of excitation and inhibition and reducing the risk of electrical stimulus artifacts.

Much of this work was conducted with rats rendered hemiparkinsonian by injection of 6-hydroxydopamine (6-OHDA). Specific neural targets were studied in the context of a range of stimulation frequencies. These studies generally validated the ability of this technique to isolate neural circuits participating in parkinsonian symptom expression while directing future studies toward potential therapeutic targets. For example, one notable finding was the importance of deep V neurons as mediators of impaired cortical stimulation.

Importantly, the authors found very different effects among the same cell types when stimulated at different frequencies, suggesting that precision is needed for both reaching the targets and providing the optimal degree of stimulation. This area of study may lead to improvements in DBS efficacy in Parkinson's disease and in other neurological disorders, such as epilepsy.

Commentary:

Jay L. Shils, PhD
Director of Intraoperative Monitoring
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This is the first significant publication explaining a novel technique that has the potential to improve DBS in the treatment of PD and other neurological diseases by offering a method which can improve our understanding of the mechanism of DBS action.

Although DBS has been helpful in many patients, its exact therapeutic effects have been unclear because the artifacts produced by stimulation obscure the ability to observe local circuit responses. With this approach, using optical stimulation, the problem of artifacts is circumvented. This provides an important opportunity to identify with some precision which neural circuits are involved.

In the studies discussed in this paper, the effects seem extremely focal, although the authors cautioned that their observations so far do not rule out the influence of oscillations outside of cell types they evaluated. The studies appear to have been well performed and very promising, but the research so far has been confined to rodents. The next step will be to reproduce these findings in a primate model, where the volume of brain is greater. However, these initial studies were well conducted and substantiate previous theories about the role of DBS. If the findings are reproduced in primates, this could conceivably yield changes in how DBS is applied, particularly with the current advances in micro-optics and lasers that should facilitate this work. ■

Mutant LRRK2^{R1441G}BAC transgenic mice recapitulate cardinal features of Parkinson's disease.

First Author and Institution:
Yanping Li, MD, Weill Medical College of Cornell University, New York, New York.

Citation:
Nature Neuroscience. 2009;12:826-828.

Objective:
Validate experimental model of leucine-rich repeat kinase 2 (LRRK2) mutation for Parkinson's disease (PD).

Type of Study:
Transgenic mouse model study.

Result:
Like the LRRK2 mutation in man, which is associated with a familial form of PD, LRRK2 transgenic mice demonstrate classical features of PD.

Conclusion:
The similarities in dopamine neuron loss and parkinsonian signs in LRRK2 mice suggest this animal model will be useful for studies of pathogenesis and therapeutic modalities.

A series of studies published in 2004 established mutations in the LRRK2 gene as the most common genetic cause of familial and nonfamilial PD. Most people with the LRRK2 mutations demonstrate dopamine neuron loss in the substantia nigra as well as Lewy body pathology. Patients with PD and LRRK2 mutations have clinical features that are generally indistinguishable from PD due to other causes.

The authors of this study developed a LRRK2 mouse model by introducing a human bacterial artificial chromosome (BAC) containing LRRK2 carrying R1441G, a common missense mutation. Transgene expression was detected in several tested areas of the central nervous system (CNS), including the striatum. Three months after birth, the genetic mutation had not produced any abnormalities in body weight, brain weight, or motor activity. However, by 10 to 12 months, most LRRK2^{R1441G} mice, unlike non-transgenic littermates and wild-type LRRK2 mice, displayed age-dependent and progressive hypokinesia and other classic signs of PD. Administration of levodopa and apomorphine reversed the motor deficits.

The transgenic mice were then evaluated with intrastriatal microdialysis to confirm loss of dopamine. Although no decrease in dopamine cell number or in organization was found among the LRRK2^{R1441G} mice versus controls, the LRRK2^{R1441G} transgenic mice had profound abnormalities at the cellular levels in dopamine neurons, including dystrophic neurites. Like some patients with PD associated with LRRK2 mutations, the mouse model also developed abnormalities of tau.

According to the authors, this mouse model successfully reproduces the motor, neurochemical, and some of the histopathological features of the LRRK2 mutation in humans. They speculate that the mouse model may not only be useful for better understanding the pathology of genetic PD but also for improving therapeutic development.

Commentary:

Claire Henchcliffe, MD, DPhil
Director, Movement Disorders Institute
Weill Medical College of Cornell University
New York, New York

This is the first animal model based on human PD genetics to demonstrate critical features consistent with clinical PD, including a progressive hypokinetic phenotype responsive to dopamine replacement, decreased intrastriatal dopamine, and dystrophic striatal axons and neurites. Although PD appears to be linked to an inherited genetic mutation in only a proportion of patients, development of relevant genetic models is critically important to better understand general PD pathophysiologic processes. Similarly, it is possible that therapies that prove effective for treating LRRK2-associated PD may also be active in non-inherited forms of PD, making this model's implications for development of future therapeutics potentially far-reaching.

One concern is that the LRRK2^{R1441G} transgenes did not demonstrate robust dopamine neuronal cell loss or Lewy body pathology, in contrast to typical PD pathology, and so more work is needed to reconcile why this is so. However, establishment of this mutant LRRK2 transgenic mouse model for PD has substantial potential for moving the field forward. Although not immediately relevant to clinical practice, the hope is that this, or other models to be developed, will serve as the "new MPTP," overcoming one obstacle in translating therapies from the laboratory to the bedside, and stimulating advances in understanding and treating PD. ■

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