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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, the first issue of *Parkinson's Disease Monitor and Commentary* for 2010, we again mix forward-looking basic science studies with clinical trials that have immediate practical applications. On the basic science side, Dr. Connie Marras of the University of Toronto evaluates the recently published evidence that glucocerebrosidase (GBA) mutations may explain 15% of cases of Parkinson's disease (PD) in patients of Ashkenazi Jewish descent. New data confirming the ability of neurons to transmit α-synuclein to promote PD and other neurogenerative diseases is the focus of a commentary by Dr. Joseph Savitt of the Johns Hopkins University School of Medicine. Each of our commentators touch on how these basic science advances might translate into new therapeutic targets.

On the practical side, Dr. Daniel Weintraub of the University of Pennsylvania critiques the data that explains why clinicians need to increase their attention to cognitive impairment in patients with PD, while Dr. Laura Marsh, who recently moved to the Baylor College of Medicine, comments on one of the first prospective studies to evaluate antidepressants in PD. Perhaps the most important message from this study is that although depression is a common complication of PD, the evidence-based data on treatment is extremely limited. Finally, I contribute a commentary on new evidence that the endogenous antioxidant urate is neuroprotective and may provide a strategy for modifying risk of PD, while Dr. Tanya Simuni of Northwestern University looks at the inroads being made with imaging for early differentiation of parkinsonian syndromes.

While we always encourage our readers to consult the original papers for a topic they find of particular interest, our commentaries are designed to provide insight and perspective from an independent source. By matching specific subject areas with an appropriate expert, our format provides a context that may not be otherwise readily available. As always, comments and suggestions are welcome. Please feel free to reach me at info@delmedgroup.com.

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In This Issue:

PD Monitor & Commentary

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Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease.

First Author and Institution:
Ellen Sidransky, MD, National Human Genome Research Institute, Bethesda, Maryland.

Citation:
New England Journal of Medicine. 2009;361: 1651-1661.

Objective:
Evaluate frequency of glucocerebrosidase (GBA) mutations in patients with Parkinson's disease (PD).

Type of Study:
Prospective genotyping analysis.

Result:
Among non-Ashkenazi participants, GBA mutations were found in 3% of patients and <1% of controls, rising to 15% and 3%, respectively, in Ashkenazi participants, producing an odds ratio for any GBA mutation of 5.4.

Conclusion:
This study validates GBA mutations as a risk factor for PD.

Several studies have associated mutations in the gene encoding the lysosomal enzyme GBA with parkinsonism. In this collaborative study, genotyping of GBA mutations was performed in 5,691 PD subjects and 4,898 controls. All centers were able to reliably confirm the presence or absence of N370S and L444P. Separate analyses were performed to identify these two mutations, other GBA mutations, and the entire coding sequence. Results were stratified on the basis of non-Ashkenazi and Ashkenazi Jewish familial heritage.

In the non-Ashkenazi group, the N370S or the L444P GBA mutation was found in 3% of the PD subjects versus <1% of controls. In the Ashkenazi group, at least one of these mutations was identified in 15% of patients versus 3% of controls. However, in the 1,883 non-Ashkenazi patients with PD who were fully sequenced, a GBA mutation was identified in 7%, suggesting that up to 45% of mutant alleles are missed without full sequencing.

Commentary:

Connie Marras, MD
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This study is an important validation of GBA mutations as a risk factor for PD. These data tell us that the presence of a GBA mutation may explain a significant component of susceptibility to PD in 1 out of every 6-7 Ashkenazi Jewish patients and 1 out of every 30 non-Ashkenazi Jewish patients.

Even though this study makes a meaningful contribution to characterizing the genetics of PD, it does not have any immediate clinical implications. Most patients with PD will not have this mutation, so we cannot rule out a risk for PD in the absence of a GBA mutation, and we do not yet know its penetrance, so the lifetime risk of someone who has a GBA mutation is unknown. It is also important to note that testing for these mutations is highly labor intensive. Without full sequencing, nearly half of the mutations are missed. This may limit the role for genetic testing in the short term. Still, the underlying pathogenic mechanism triggered by a GBA mutation is relevant to a sizeable minority of patients, so this may be an important focus for understanding the causes of this disease. At this point, it is not clear what the mechanism is by which GBA mutations increase the risk of PD. These data do provide a firm justification for pursuing this avenue of research and may provide important insights into the pathogenesis of idiopathic PD as well. ■

Urate as a predictor of the rate of clinical decline in Parkinson disease.

First Author and Institution:
Alberto Ascherio, MD, Harvard University School of Public Health, Cambridge, Massachusetts.

Citation:
Archives of Neurology. 2009;66:1460-1468.

Objective:
Evaluate whether serum or cerebrospinal fluid (CSF) levels of urate can predict progression of Parkinson's disease (PD).

Type of Study:
Prospective secondary analysis of a double-blind, randomized trial of the antioxidant treatments deprenyl and tocopherol in PD.

Result:
Progressive disease was inversely correlated with increasing baseline levels of both serum and spinal fluid urate concentrations overall, but the effect was lost in those randomized to tocopherol.

Conclusion:
The study supports a potential benefit from raising urate levels in patients with PD, but due to the risks of elevated urate levels, the risk-to-benefit ratio of such a strategy will require careful evaluation.

Urate, a potent endogenous antioxidant, has a theoretical potential to protect against neurodegenerative processes such as PD by mediating against oxidative damage.

Over the course of the double-blind DATATOP (Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism) trial, serum and CSF urate concentrations were measured before patients with PD were randomized to receive the monoamine oxidase (MAO) type B inhibitor deprenyl, the antioxidant tocopherol (vitamin E), or both. The relationship between baseline urate levels and clinical course was evaluated in the substudy presented here.

Relative to the quartile with the lowest serum level of urate at baseline, the quartile with the highest level had a 36% lower risk (Hazard Ratio [HR] 0.64, 95% Confidence Interval [CI] 0.44-0.94) for progressing to the primary endpoint of clinical disability requiring levodopa therapy. For each standard deviation increase in serum urate level, the risk of the primary endpoint was reduced by 18% (HR 0.82, 95% CI 0.73-0.93). When stratified by treatment, the association between increased urate levels and lower risk of progression was observed only in those who did not receive tocopherol. The latter finding suggests an interaction occurs between urate and tocopherol. Similar results were demonstrated with CSF urate levels.

Raising urate levels has numerous risks, including the potential for the development of hypertension, coronary artery disease, and stroke, but these data indicate that further studies are warranted.

Commentary:

Andrew D. Siderowf, MD
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*In this secondary analysis of the DATATOP cohort, Ascherio and colleagues show that higher urate levels in both the serum and the CSF were associated with slower progression of PD. In this study, subjects with the highest blood and CSF urate levels were nearly half as likely to require rescue dopaminergic treatment as those with lower urate levels. The results extend similar findings by the same authors in a secondary analysis of the PRECEPT clinical trial. In this earlier analysis, Schwarzschild and colleagues (*Arch Neurol. *2008;65:716-723) showed that higher urate levels were associated with slower progression of PD, both clinically and based on change in dopamine transporter imaging.*

The current study is important for several reasons. First, it confirms that urate may have neuroprotective properties in PD, both when measured in the blood and the CSF. Urate may exert this effect through antioxidant properties, and a clinical trial based on the possible protective effects of raising urate levels is currently underway. Second, higher urate levels were only associated with slower disease progression in subjects who were not receiving treatment with vitamin E. This interaction between urate and vitamin E is consistent with the antioxidant properties of both compounds and suggests that vitamin E, which was not effective as a treatment in the DATATOP study, may have biological activity in certain patient subgroups. ■

Dementia and survival in Parkinson's disease: a 12-year population study.

First Author and Institution:
T C. Buter, MD, Norwegian Centre for Movement Disorders, Stavanger, Norway.

Citation:
Neurology. 2008;70:1017-1022.

Objective:
Evaluate the long-term incidence of dementia and predictors of survival related to dementia in patients with Parkinson's disease (PD).

Type of Study:
Prospective, longitudinal, population-based cohort study.

Result:
The cumulative incidence of dementia in patients with PD increases with age, reaching 60% within 12 years of follow-up. Older age, longer duration of PD, and male sex are risk factors for development of dementia.

Conclusion:
Not only do the majority of patients with PD develop cognitive impairment, but survival after developing dementia is often protracted.

Declining cognitive function is common in patients with PD, but there has been limited information about the relationship between onset of motor symptoms and onset of cognitive loss, or the duration of survival in patients with PD after cognitive loss develops.

In this prospective, longitudinal cohort study, 233 patients with PD in Norway without dementia at baseline were evaluated for cognitive loss over time. Dementia was defined by criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* (DSM-IIIR).

A dementia prevalence of 80% to 90% was projected by age 90.

After 12 years of follow-up, 140 (60%) of the patients had developed cognitive loss (95% Confidence Interval [CI], 54%-66%). There was a steady increase in the risk of dementia with both age and the duration of PD. The authors calculated that a male patient with PD and no dementia at age 70 would, on average, survive for 8 years, of which the final 3 years would be in a demented state. Women with PD, who live longer on average (11 years), would be expected to have a longer period of survival in a demented state (3.8 years). A dementia prevalence of 80% to 90% was projected by age 90.

Due to the high frequency of dementia in patients with PD and the anticipated role of this complication in diminishing quality of life, reducing patient independence, and increasing demand for services, this study suggests the need for specific accommodations for cognitive loss to improve PD management.

Commentary:

Daniel Weintraub, MD
Associate Professor of Psychiatry and Neurology
Consultant Psychiatrist, Parkinson's Disease Centers
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In addition to the data already published on the risk of dementia in patients with PD, most clinicians who work with patients with PD are aware that dementia is a common complication in this population. This study does not break new ground in that regard, but it helps quantify the problem in a more rigorous way than previous studies that have produced similar results. For example, the enrollment of patients with PD but without dementia allowed the authors to show prospectively that increasing age and a longer duration of PD are risk factors. The evidence that patients with PD survive for considerable periods after they develop dementia was another notable feature of this study. However, the patients had a median duration of PD of 8 years at entry with a considerable range, so the estimated risk of PD duration on development of dementia was a rough rather than a precise estimate.

Although the main results of the study are not surprising in any way, they do provide another opportunity to stress that dementia is a common complication of PD and that clinicians should be routinely screening patients for cognitive impairment. Clinicians need to consider how to manage all stages of cognitive dysfunction, and we should evaluate any new medications for the motor symptoms of PD for their acute and long-term effects on cognitive performance. ■

A controlled trial of antidepressants in patients with Parkinson's disease and depression.

First Author and Institution:
Matthew Menza, MD, Robert Wood Johnson Medical School, Piscataway, New Jersey.

Citation:
Neurology. 2009;72:886-892.

Objective:
Compare antidepressant medications in patients with Parkinson's disease (PD) and depression.

Type of Study:
Randomized, placebo-controlled trial.

Result:
In a three-way comparison, nortriptyline was significantly more effective than both paroxetine and placebo for control of depression in patients with PD. Paroxetine was not superior to placebo.

Conclusion:
The finding that a tricyclic antidepressant but not a selective serotonin reuptake inhibitor (SSRI) is effective against depression associated with PD is unexpected and deserves further study.

Depressive disorders are a common complication of PD, occurring in up to 50% of individuals in some series. Some investigators report that depression is a more important predictor of impaired well-being than motor symptoms.

Fifty-two patients with PD and depressive disorders were randomized to receive the tricyclic antidepressant nortriptyline, the SSRI paroxetine in a controlled-release (CR) formulation, or placebo. Patients were excluded from the study if they had significant cognitive impairment, a psychiatric diagnosis other than depression or anxiety, or prolonged off periods. The primary outcome measures were change in the Hamilton Depression Rating Scale (HAM-D) and response rate.

After 8 weeks of treatment, the advantage of nortriptyline for reducing HAM-D scores was significant relative to placebo ($P<0.002$). There were no significant differences between the placebo and paroxetine-CR treated groups. Response rates also favored nortriptyline ($P<0.05$): 53% for nortriptyline, 11% for paroxetine-CR, and 24% for placebo. While nortriptyline was also superior to placebo for a variety of secondary outcomes, including anxiety and social functioning, paroxetine-CR was not.

Compared to placebo, side-effect rates were similar for the nortriptyline group, but higher for the paroxetine-CR group ($P=0.028$).

There is no definitive explanation for the greater superiority of nortriptyline relative to paroxetine in patients with PD, but it is possible that the critical mechanisms of depression associated with PD involve noradrenergic dysfunction. Larger studies with longer follow-up are needed to confirm these results.

Commentary:

Laura Marsh, MD
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Depression is a common, frequent, and clinically important complication of PD. Although this study was small and conducted over a period of only 8 weeks—which is a shorter period than commonly employed in trials of antidepressants in individuals without PD—it represents a needed effort to evaluate the efficacy of existing therapies. The authors wisely excluded such characteristics as cognitive impairment and other factors that might have complicated interpretation of results. However, it is notable that seven of the 18 patients on paroxetine, or almost 40%, withdrew from the study before it was completed. This limits our conclusions about efficacy, and, despite these results, I do not think that nortriptyline should now necessarily be considered the first-line antidepressant. Although it was effective and well tolerated—and nortriptyline has the advantage of being relatively inexpensive—it is also more complicated to use, particularly in an elderly PD population that may be more susceptible to muscarinic side effects or QTc prolongation (although no electrocardiographic disturbances were seen in this study).

In clinical practice, the goal of depression treatment should be complete remission of the depressive episode, and not just a reduction in symptoms, which was the endpoint in this study. Importantly, however, this study provides evidence that antidepressants are beneficial in PD and should reinforce efforts to identify and treat this common PD complication. ■

Inclusion formation and neuronal cell death through neuron-to-neuron transmission of α-synuclein.

First Author and Institution:
Paula Desplats, MD, University of California at San Diego, California.

Citation:
PNAS. 2009;106:13010-13015.

Objective:
Explore the possibility that α-synuclein can be transferred between cells in a cell culture and a live animal model.

Type of Study:
Basic research with in vivo mouse and cell culture models.

Result:
Neuronal cells take up α-synuclein through endocytosis to develop α-synuclein pathology. Both in vivo and in vitro data suggest that uptake of α-synuclein can be toxic to the recipient cell.

Conclusion:
The transference of α-synuclein pathology between cells may play a role in the progression of Parkinson's disease (PD) as well as help explain the acquisition of α-synuclein pathology in transplanted fetal cells.

Aggregation of the protein α-synuclein has been associated with several neurodegenerative disorders, including PD. Aggregates of α-synuclein comprise much of Lewy bodies, the pathological hallmark of PD, and mutations in the gene encoding α-synuclein have been linked to forms of parkinsonism. It has been theorized that this protein has the potential to spread among neurons and that this process may be a major factor in progressive neurodegeneration.

In a series of cell culture studies, the authors showed that α-synuclein is taken up by neurons through endocytosis. Moreover, the authors demonstrated that this uptake occurs in grafted mouse cortical stem cells that have been transplanted into α-synuclein over-expressing mouse brain, thus showing that neuronal transplants are at risk of acquiring host pathology. Additional studies suggested that cell-to-cell contact is not necessary for transmission of α-synuclein since condition media can transmit the pathology as well.

The authors cite studies that have demonstrated this idea of inter-neuronal spread of pathology in conditions such as Alzheimer's disease, prion diseases, and polyglutamate diseases. In addition to the transmission of α-synuclein between cells, the authors further demonstrated in their model that there is greater intracellular accumulation of α-synuclein when lysosomes are inhibited. They suspect that decline in lysosomal function is a contributing factor in the infection-like process that encourages spread of α-synuclein between cells.

Based on these studies, both the production and uptake of α-synuclein may be potential targets for prevention or treatment of PD and other neurodegenerative disorders.

Commentary:

Joseph Savitt, MD, PhD
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Histological and genetic evidence suggests that α-synuclein is an important pathogenic factor in PD. This study by Desplats et al builds on previous data supporting the idea that α-synuclein can be transferred from one cell to another and that this process may provide a mechanism for the spread and progression of PD pathology in the brain.

This theory has no immediate clinical application because there are no current treatments available to interrupt this process. It does, however, identify a number of potential treatment targets against which therapies might be developed. While such targets currently include the blockade of α-synuclein production or aggregation, this study suggests that the blockade of α-synuclein release, the sequestration of free α-synuclein in the extracellular environment, the blockade of α-synuclein cellular uptake, and the enhancement of lysosomal function also may be valid targets. Additionally, the notion that α-synuclein can be transferred from a sick cell to a healthy cell has implications for potential cell transplant therapies, as the donor tissue may become "infected" by abnormal aggregates of α-synuclein present in the cellular environment. Indeed, this may be the explanation for the acquisition of premature PD pathology that has been noted in recent human fetal transplant autopsy studies. ■

Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis.

First Author and Institution:
Chris C. Tang, MD, The Feinstein Institute for Medical Research, Manhasset, New York.

Citation:
Lancet Neurology. 2010;9:149-158.

Objective:
Evaluate positron emission tomography (PET) imaging for distinguishing different types of parkinsonism.

Type of Study:
Uncontrolled case series.

Result:
PET imaging has an 84%-88% sensitivity and 94%-97% specificity for distinguishing parkinsonian syndromes.

Conclusion:
This study validates PET imaging as a tool to differentiate parkinsonian disorders in order to more accurately counsel patients and to initiate appropriate treatment more rapidly.

The major clinical features of Parkinson's disease (PD) are shared by several other parkinsonian conditions, such as progressive supranuclear palsy and multiple systems atrophy. Early diagnosis of PD and atypical parkinsonian disorders is important for providing an accurate prognosis to patients, for initiating appropriate therapy, and for selecting patients for neuroprotective clinical trials. Several studies suggest that imaging of the central nervous system may be able to differentiate disease states even when clinical features cannot.

In this study, 167 patients with parkinsonian features were evaluated with fluorine-18-labelled fluorodeoxyglucose-PET (FDG-PET) over an 8-year period at a single institution. An automated system for differentiating idiopathic PD, multiple system atrophy, and progressive supranuclear palsy was employed to classify each patient. After imaging, patients were followed clinically for a mean of 2.6 years. Final clinical diagnosis served as the gold standard.

For distinguishing between PD and other parkinsonian syndromes, the PET imaging classification system had a sensitivity of 84% and a specificity of 97%. For arriving at an accurate diagnosis, the system had a negative predictive value of 82% and a positive predictive value of 98%. The specific sensitivities and specificities for each of the three diagnoses when assessed individually as well as the negative and positive predictive values were in a similar range.

Although the accuracy of this system is confined to the three parkinsonian disorders included in this study, the authors are now evaluating FDG-PET image characteristics for other entities. The authors contend that this will be a valuable diagnostic tool if validated in prospective studies by other centers.

Commentary:

Tanya Simuni, MD
Associate Professor of Neurology
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Northwestern University
Chicago, Illinois

This is a very well conducted and important study that confirms work published previously by the same group with a smaller number of patients. Clearly, there is a clinical need for more rapid methods of accurately distinguishing between parkinsonian disorders. The frequency of misdiagnosis of parkinsonian diseases ranges up to 25% in some series. For the three major syndromes these authors evaluated, both the specificity and the sensitivity were encouraging. However, it is important to recognize that this study was conducted by a highly experienced group of investigators. Although their technique is automated, it will be important to confirm that a similar degree of diagnostic accuracy can be achieved by less experienced centers. It is also important to consider that other imaging techniques, particularly novel magnetic resonance imaging (MRI) sequences, are now being evaluated to similarly distinguish between parkinsonian disorders. It is not known whether these will produce a similar degree of diagnostic accuracy, but MRI is more widely available and might be employed more rapidly as a standard if the accuracy was acceptable.

While reproducibility will be an important next step in bringing FDG-PET closer to use as a routine tool in the early diagnosis of parkinsonian disorders, it is likely that this type of approach will prove useful for more rapidly distinguishing the different disease states, addressing an important clinical need. ■

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