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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 the first 2009 issue of *Parkinson's Disease Monitor and Commentary*, we again attempt to place new research into a clinical context for the practicing physician. We tackle subjects ranging from a landmark comparison of deep brain stimulation relative to medical therapy to evolving data on therapies that could slow disease progression. In every case, we invite those who have specific expertise in the subject area to tell us whether the findings are new, relevant, interesting, and of potential clinical value.

One of the most active areas of research in Parkinson's disease (PD) is the development of imaging tools with potential diagnostic or prognostic value. We have two articles that address this issue. Dr. Paul Tuite of the University of Minnesota critiques new research on diffusion tensor imaging (DTI) as a tool for early diagnosis of PD, while Dr. Danna Jennings of the Institute for Neurodegenerative Disorders in New Haven evaluates a study on FP-CIT SPECT for the same indication.

The goal of our commentaries is not just to summarize information that can just as easily be drawn from the abstract but to provide a context from an expert who can identify strengths and weaknesses. We hope the format can help clinicians stay in touch with on-going research initiatives. Even if readers choose to go the original source to learn more, we hope the commentaries provide an orientation for considering the findings.

Comments and suggestions are welcome. Please send them to me in care of info@delmedgroup.com.

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In This Issue:

PD Monitor & Commentary

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Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: A 3-year multicenter study with repeat [^{123}I]FP-CIT SPECT.

First Author and Institution:
Vicky L. Marshall, MD, Southern General Hospital, Glasgow, Scotland, United Kingdom.

Citation:
Movement Disorders 2008; Epub ahead of print.

Objective:
Evaluate sensitivity and specificity of FP-CIT single-photon emission tomography (SPECT) imaging for early diagnosis of Parkinson's disease (PD).

Type of Study:
Prospective, multicenter, nonrandomized, longitudinal study.

Result:
On-site clinical diagnosis including FP-CIT SPECT overdiagnosed PD at baseline in diagnostically uncertain cases relative to the gold standard clinical evaluation at 36 months.

Conclusion:
Dopamine transporter imaging using FP-CIT SPECT may have a role in specialized cases, but is not a substitute for clinical evaluation.

Diagnosing PD on the basis of clinical features provides a reasonable specificity and sensitivity when performed by specialists. However, objective markers of the presence of PD are being sought to improve diagnostic accuracy in individuals with early symptoms or when atypical features delay diagnosis.

Several published studies have suggested that dopamine transporter imaging with FP-CIT SPECT may serve as a useful diagnostic tool for PD. In some studies, a reduction in dopamine transporter density has been detected prior to the onset of motor symptoms. In this prospective study, FP-CIT SPECT was compared with clinical diagnosis at a specialty center in patients with tremor or other symptoms that suggested PD but for whom there was diagnostic uncertainty. The relative diagnostic accuracy of this tool and clinical assessment was assessed at 36 months of follow-up in 99 patients and three healthy volunteers.

The sensitivity and specificity of clinical diagnosis was 93% and 46%, respectively, versus 78% and 97% for FP-CIT SPECT. Inter-reader agreement on scans read by blinded investigators was high.

Commentary:

Danna Jennings, MD
Clinical Research Director
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New Haven, Connecticut

This study demonstrates that FP-CIT SPECT imaging offers a higher specificity for the diagnosis of PD than the baseline clinical evaluation. An important finding of this study is that more than 50% of the participants with normal FP-CIT SPECT results at baseline carried a diagnosis of PD by the initial clinical diagnosis at a specialty clinic. While these subjects were referred into the study with diagnostic uncertainty, there was a clear tendency to overdiagnose PD in this population, which could result in inappropriate treatment. While other studies have shown similar results, the strength of this study is that it provides the longest prospective follow-up of the diagnostic accuracy of dopamine transporter imaging in PD. In addition, it importantly compared FP-CIT SPECT and clinical evaluation at a specialty clinic, where the accuracy of a clinical assessment would be expected to be most accurate.

Although dopamine transporter imaging cannot take the place of a clinical evaluation, it can offer useful diagnostic information when used in combination with the clinical evaluation. As someone with a research interest in imaging, I see the current role of dopamine transporter imaging as providing additional information in patients with subtle symptoms too early in the course to diagnose and in patients with atypical presentations. ■

Long-term outcome of early versus delayed rasagiline treatment in early Parkinson's disease.

First Author and Institution:
Robert A. Hauser, MD, University of South Florida, Tampa, Florida.

Citation:
Movement Disorders. 2008; Epub ahead of print.

Objective:
Evaluate the long-term benefit of early versus delayed treatment of Parkinson's disease (PD) with rasagiline

Type of Study:
Open-label extension of a double-blind randomized trial.

Result:
Significantly less worsening of symptoms on Unified Parkinson's Disease Rating Scale (UPDRS) scores was observed at all timepoints up to 6.5 years among those started early on rasagiline versus those who received delayed rasagiline.

Conclusion:
Early initiation of rasagiline provides long-term benefit.

When a double-blind, randomized trial called TEMPO (*Arch Neurol.* 2002;59:1937-1943) associated early initiation of rasagiline, a selective inhibitor of monoamine oxidase type B (MAO-B), with a reduction in the worsening of PD symptoms, the authors speculated that the benefit of rasagiline was not limited to symptoms but that it also slowed clinical progression. In the initial study, 1 mg/day and 2 mg/day rasagiline produced UPDRS scores at 12 months that were 1.82 and 2.29 units less (indicating less worsening), respectively, than those of subjects who were randomized to 6 months of placebo therapy before starting on 2 mg/daily rasagiline (P=0.05 and P=0.01, respectively).

To evaluate the long-term effects, patients who completed the TEMPO study were invited to enroll in an open-label extension. Of the 177 patients followed for at least 5 years in the extension program, 114 were in the early treatment group and 63 were in the delayed treatment group. In the extension study, patients received 1 mg/daily (after an early protocol change that switched patients from the initial dose of 2 mg/daily).

The advantage of early treatment over delayed treatment persisted throughout the study. At the latest follow-up at 6.5 years, the advantage for early treatment was 2.5 UPDRS units change from baseline in favor of the early-start group (P=0.021), corresponding to a 16% mean relative difference from baseline between groups (P=0.006). There was no difference in motor complications or dopaminergic side effects from early initiation of rasagiline. The authors speculate that the advantage of an early start may be due to endogenous compensatory mechanisms or a neuroprotective effect.

Commentary:

Daniel E. Kremens, MD, JD
Assistant Professor of Neurology
Jefferson Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania

This is an important and well-designed study that should lead to a change in practice because it substantiates evidence that early initiation of rasagiline continues to provide a clinical advantage over the long term. Although this was an open-label study, which does not provide the strength of a double-blind evaluation, such controlled trials are difficult to perform over the length of time of this investigation. However, this extension was anchored by a double-blind study and is consistent with the more recently completed double-blind ADAGIO study (Rascol et al, 12th Congress of the European Federation of Neurological Societies, in Madrid, Spain).

The advantage of early treatment over delayed treatment persisted throughout the study.

Although the ADAGIO data have not yet been published, the abstract of this multinational study, which randomized more than 1,000 patients, also associated rasagiline with a delay in progression if initiated early. The fact that the patients who received early rasagiline in the TEMPO extension are still doing better 6 years later even though rasagiline was started just 6 months later in the delayed treatment group suggests that this MAO-B inhibitor is probably doing something more than just delaying symptoms. Whether or not this agent has important neuroprotective effects, as suggested by experimental studies, or is facilitating a compensatory mechanism, the cumulative data do reinforce the importance of early treatment for both early and late benefit. ■

Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: A randomized controlled trial.

First Author and Institution:
Frances M. Weaver, PhD, Hines VA Hospital, Hines, Illinois.

Citation:
Journal of the American Medical Association. 2009;301:63-73.

Objective:
Compare motor outcome at 6 months in patients with advanced Parkinson's disease (PD) receiving deep brain stimulation (DBS) versus best medical therapy.

Type of Study:
Prospective, controlled, and randomized trial.

Result:
Patients randomized to DBS gained almost 5 hours of "on" time without troublesome dyskinesias compared with patients receiving best medical therapy, but the DBS subjects had more serious adverse events.

Conclusion:
The balance between the benefits and risks of DBS deserves further study, and the decision to provide DBS should be individualized for each patient.

Over the past 15 years, despite little controlled data, DBS has become a common intervention for patients with advanced PD who are no longer adequately controlled on medical therapies.

This study compared outcomes over 6 months in 255 patients with advanced PD. One hundred and thirty-four received best medical therapy and 121 received DBS (60 had bilateral DBS of the subthalamic nucleus and 61 had DBS of the globus pallidus).

When compared with the best medical therapy group, patients randomized to DBS gained 4.6 more hours (P<0.001) in the "on" state without troubling dyskinesias. They were also more likely to achieve a ≥5 point improvement in the Unified Parkinson Disease Rating Scale (UPDRS) (71% versus 32%; P<0.001). However, DBS patients were more likely to experience decrements in neurocognitive functioning, and their rate of serious adverse events was much greater (49 versus 15 patients with 82 and 19 events, respectively).

Although DBS is effective, as suggested in previous uncontrolled studies, it is not without risks. More data are needed on relative improvements in quality of life. The investigators suggest that the decision to provide DBS should be individualized for each patient.

Commentary:

Kelvin L. Chou, MD
Assistant Professor of Neurology and Neurosurgery
University of Michigan Medical School
Ann Arbor, Michigan

This study is important because it shows that DBS improves motor function, "on" time without troubling dyskinesias, and quality of life in PD patients at 6 months compared with best medical therapy, utilizing a blinded assessment trial design. This will probably be as close to the "gold standard" double-blind, placebo-controlled, randomized design that a DBS trial can get without resorting to sham surgery. Moreover, approximately 1/4 of the participants in this trial were older than 70, and the motor benefit experienced by this group was similar to that seen in younger patients. Previous DBS studies tended to include only younger patients, which make the findings in this trial more applicable to the typical PD patient seen in the clinic.

Although DBS is effective, as suggested in previous uncontrolled studies, it is not without risks.

The risk of an adverse event in this trial, however, was 3.8 times higher in the DBS group, with older patients more likely to experience adverse events than younger patients. Although it was previously known that DBS was associated with more risks than medical therapy, the number of patients in this study experiencing an adverse event is higher than previous reports, so potential candidates must continue to be screened carefully. The risks and benefits of DBS should be explained to PD patients clearly and without bias, so they can make an educated and informed decision.

Finally, it should be noted that these results were obtained at experienced DBS centers. Despite the wide acceptance of DBS for PD and the great clinical benefits that can be obtained, clinicians should still be cautious about sending potential surgical candidates to a place without DBS-trained neurologists and neurosurgeons. ■

High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson disease.

First Author and Institution:
David E. Vaillancourt, PhD, University of Illinois at Chicago, Chicago, Illinois.

Citation:
Neurology. 2009; Epub ahead of print.

Objective:
Evaluate high-resolution diffusion tensor imaging (DTI) of dopamine as a method of diagnosing early- stage Parkinson's disease (PD).

Type of Study:
Blinded reading of imaging in a small number of patients and controls.

Result:
The authors report 100% sensitivity and specificity for DTI in distinguishing PD patients from healthy controls with findings consistent across two blinded readers.

Conclusion:
High-resolution DTI shows promise as a non-invasive tool for identification of early-stage PD.

DTI, which has been used to evaluate pathophysiologic changes in white matter, can track dopaminergic degeneration by evaluating change in the direction, or the anisotropy, of water molecules. In late stages of PD, the change in fractional anisotropy of the substantia nigra appears to be due to changes in microstructural integrity and diffusivity of water molecules.

To test whether high-resolution DTI is a reliable non-invasive tool for detecting early-stage PD, 14 patients with early and untreated PD and 14 age- and gender-matched controls were evaluated. The imaging was conducted in rostral, middle, and caudal regions of the substantia nigra and then evaluated by blinded independent raters. The raters were looking for characteristic changes in fractional anisotropy that would suggest dopaminergic degeneration.

The reduction in the fractional anisotropy of patients versus controls was highly statistically significant ($P<0.001$). The relative differences were greatest in the caudal region, where the sensitivity and specificity for PD in patients relative to controls was 100% for both independent raters.

This is not the first study to demonstrate that DTI can distinguish differences in the substantia nigra of PD patients relative to controls, but the authors identify it as the first demonstration in early-stage PD among patients who are not taking dopaminergic medication. The authors suggest a study is now needed to compare DTI to the gold standard of a clinical evaluation by a neurologist. If additional studies validate these findings, there are numerous potential applications, including definitive studies in suspected PD with atypical symptoms or preclinical evaluation of the presence of dopaminergic degeneration.

Commentary:

Paul Tuite, MD
Director of the Movement Disorders Center
University of Minnesota Medical Center
Minneapolis, Minnesota

DTI is promising, but there are several reasons to believe that this technology is not ready for routine clinical use.

First, the 3 Tesla (T) magnetic resonance imaging (MRI) machine used in this study is stronger than the 1.5T magnets available in most clinics. The 3T devices will eventually be ubiquitous, but access is now limited.

Secondly, standardized methods are needed to automatically select the substantia nigra on MRI scans in order to make this more easily implemented, as now time and expertise is required after collection of imaging data. This will require software developments, which will be challenging.

Thirdly, each MRI machine needs to be calibrated for normative age- and gender-matched control values to allow for comparison with a single individual's result to determine if they have a normal or abnormal value.

Finally, despite the outstanding sensitivity and specificity in this study, the findings are probably not specific to PD but reflective of changes in fiber tracts that could occur in other parkinsonian conditions, such as multiple system atrophy, progressive supranuclear palsy, and possibly even vascular parkinsonism.

Although this paper moves DTI MRI closer to use as a diagnostic tool, as well as a means for measuring disease severity, the technology is in its formative stages. Cautious optimism is appropriate. ■

Gout and the risk of Parkinson's disease: A cohort study.

First Author and Institution:
Mary DeVera, MD, University of British Columbia, Vancouver, Canada.

Citation:
Arthritis and Rheumatism. 2008;59:1549-1554.

Objective:
Evaluate relationship between gout and risk of Parkinson's disease (PD) in patients ≥65 years.

Type of Study:
Population-based cohort evaluation using Cox proportional hazard ratios to estimate the relative risk of PD.

Result:
The relative risk of PD in patients with gout was reduced by 30%.

Conclusion:
The evidence that gout is associated with a reduced risk of PD supports a protective effect from uric acid. If isolated, the mechanism of this effect may guide strategies for PD prophylaxis.

The hypothesis that high levels of uric acid, an antioxidant, confer neuroprotection and reduce the risk of developing PD has been supported by three prospective cohort and two retrospective case-control studies. Such protection, if confirmed, has potential relevance both to prophylaxis of PD and to treatment.

In the current study, the incidence of PD was compared in 11,258 gout patients aged 65 or older and 56,199 controls enrolled in a large health care database in Canada. Gout patients and controls were matched for age, sex, and length of medical record. Risk estimates for PD were adjusted for age, sex, prior co-morbid conditions, and use of diuretics and non-steroidal anti-inflammatory drugs.

In a median follow-up of 8 years, there were 1,182 new cases of PD among gout patients and controls. When gout patients and controls were compared, the relative risk for PD was 0.70 among the gout patients (95% CI, 0.59-0.83), which translates into a 30% risk reduction. This relative protection was observed for both men and women and those not taking diruetics.

The findings increase the evidence that gout provides protection against PD. Although the authors acknowledge that these data do not exclude the possibility that low serum uric acid was an epiphenomena of PD, this is considered to be unlikely in the absence of a mechanism to explain this relationship. In contrast, these data are consistent with neuroprotective effects from elevated uric acid and encourage further studies that may lead to new prophylactic or therapeutic strategies.

Commentary:

Marian L. Evatt, MD, MS
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The association between gout and the reduced risk of incident PD reported here is not new, but it adds to the body of evidence suggesting that elevated levels of uric acid may exert a neuroprotective effect relevant to PD. The consistency of evidence includes similar results provided by previous cohort and case-control studies and also from the experimental data that the antioxidant properties of uric acid preserve dopaminergic neurons. Moreover, some preliminary clinical trial data associate higher serum urate levels with slower PD progression.

Cohort studies have many limitations, but these results do encourage more definitive studies to determine whether altering uric acid levels has prophylactic or therapeutic effects. As medications become available that more effectively lower uric acid levels, this study's publication in the rheumatology (rather than neurology) literature has the potential benefit of instilling caution in aggressively treating uric acid levels. However, the association between an elevated uric acid level and a reduced risk of PD does not yet have a clear application for clinicians. For example, measuring uric acid has no practical value because there is no guidance for managing a patient based on the result. Due to the health risks of hyperuricemia, there may be a narrow window of benefit-to-risk even if uric acid is confirmed to be neuroprotective. We can only wait for more information. ■

Due to the health risks of hyperuricemia, there may be a narrow window of benefit-to-risk even if uric acid is confirmed to be neuroprotective.

Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease.

First Author and Institution:
Vanessa Brochard, MD, Hôpital de la Salpêtrière, Paris, France.

Citation:
Journal of Clinical Investigation. 2009;119:182-192.

Objective:
Identify the components of an activated immune system that participate in dopaminergic toxicity in Parkinson's disease (PD).

Type of Study:
A series of postmortem evaluations and experimental animal studies.

Result:
T-cell mediated neurotoxicity in patients with PD appears to be entirely mediated by CD4+ cells that express FasL.

Conclusion:
The evidence that peripheral T cells invading the parenchyma contribute to dopaminergic cell degeneration suggest that the adaptive immune system may be a viable target of therapy.

There is substantial evidence that the characteristic loss of dopaminergic neurons in patients with PD is at least partly due to neuroinflammatory processes. The role of the peripheral adaptive immune system in mediating disease progression has been unclear. Although upregulation of the cellular and humoral responses in the peripheral immune system has been observed, it is possible that this is simply a secondary consequence of injury to the nigrostriatal pathway.

In this report, the effort to define the role of the adaptive immune system in the etiology of PD was based on human postmortem studies and a 1-methyl-4-phenyl—1,2,3,6-tetrahydropyridine (MPTP) mouse model of neurodegeneration. The focus was on specific changes in T-cell populations and cytokines suspected of mediating or participating in dopaminergic cell death.

In the postmortem evaluations, immunohistochemical staining was able to establish infiltration of peripheral CD4+ and CD8+ leukocytes in close contact of melanized dopaminergic neurons. Positive staining was not observed for B or natural killer (NK) cells. In the MPTP mouse model of dopaminergic injury, cell death was greatly attenuated in the absence of CD4+ T cells but not CD8+ T cells. In further studies of immune reconstitution, it was found that the expression of FasL but not interferon-gamma (IFN-γ) was important for CD4+ T cells to exert a cytotoxic effect on dopaminergic neurons.

While a variety of etiologic triggers of PD have been pursued as potential targets for providing prophylaxis or treatment of this disorder, these results support the hypothesis that the innate neuroinflammatory process might also be a targetable process of PD pathogenesis.

Commentary:

John E. Duda, MD
Director, Parkinson's Disease Research, Education and Clinical Center (PADRECC)
Philadelphia VA Medical Center and
Assistant Professor of Neurology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

This is a methodologically sound study that answers some important questions, but raises many more as well.

The issue addressed by this study, like several previous studies, is whether the adaptive immune system plays a role in the neurodegeneration of PD in addition to the role played by the innate immune system. While the data from this study are consistent with previous reports that an activated adaptive immune response leads to infiltration of T cells at the site of dopamine neuron death, we still do not know whether this is an important and targetable aspect of PD pathophysiology. The problem may lie with the MPTP model and other similar acute intoxication models, which have led to several unsuccessful phase-III neuroprotective clinical trials, suggesting that these models may not be appropriate candidates for the development of these therapies. A recent study that demonstrated upregulation of an adaptive immune response in a mouse model of targeted over-expression of alpha-synuclein in the absence of frank neurodegeneration was perhaps a more compelling argument to target the adaptive immune response in PD, but further clarification of the significance of this response, including the relationship between the beneficial and deleterious aspects of immune activation for vulnerable neurons, is warranted. ■

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