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Parkinson's Disease Monitor & Commentary

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

From the editor...

ANDREW D. SIDEROWF, MD

This issue of *Parkinson's Disease Monitor & Commentary* largely concerns nonmotor complications of Parkinson's disease (PD), all of which are less likely than motor symptoms to be directly due to dopaminergic loss in the central nervous system. For example, one of our experts, Dr. Hubert Fernandez, was invited to address a new population-based study that found 60% of patients with PD followed for 12 years developed psychosis. Although this rate may seem high, Dr. Fernandez explains why it may actually be an underestimate.

Dr. James Morley, who is on the faculty with me at the University of Pennsylvania, critiques a study that found that the impairments in olfactory function seen in many patients with PD are not necessarily progressive or static over time. Rather, they fluctuate and some may even resolve. Although the sample size is small, Dr. Morley explains why this study raises considerable doubt about the use of olfactory changes as a prognostic marker in PD, as some researchers have suggested previously.

The potential for idiopathic rapid-eye-movement sleep behavior disorder (IRBD) to identify patients destined for PD or another synucleinopathy is addressed in an imaging study evaluated by Dr. Ron Postuma from McGill University. This area remains promising, but Dr. Postuma sees some limitations with the study and suggests there is some distance to go.

In another study on the research side, Dr. Claire Henchcliffe of Weill Cornell Medical Center evaluates evidence that the MAO-B inhibitor rasagiline exerts neuroprotective effects. On the practical side, Dr. Nabila Dahodwala of the University of Pennsylvania looks at a Medicare survey that suggests some elderly patients with PD are not receiving therapy, although she points out a few obstacles to leaping too quickly to this conclusion. And finally, I evaluate a study that makes a strong case for screening patients with PD for mild cognitive impairment even at early stages of disease. I concur with this finding.

For those who are interested in any of the topics addressed in this issue, we recommend consulting the original source. While we match studies with experts who know the field, our reviews are not meant to be a final analysis. 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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Use of antiparkinson medications among elderly Medicare beneficiaries with Parkinson's disease.

First Author and Institution:
Yu-Jung Wei, MS, University of Maryland School of Pharmacy, Baltimore, Maryland.

Citation:
American Journal of Geriatric Pharmacotherapy. 2010;8:384-394.

Objective:
Describe antiparkinson drug therapy use in elderly patients.

Type of Study:
Evaluation of Medicare database.

Result:
Almost half of the patients with Parkinson's disease (PD) did not take any drug for their disease.

Conclusion:
Factors that were associated with low rates of antiparkinson drug use should be considered in the development of strategies to intervene with elderly patients with PD.

In elderly patients with PD, several factors, such as inadequate health coverage and comorbidities, have been associated with a diminished likelihood of receiving treatment.

In this study, data were drawn from the self-reported Medicare Current Beneficiary Survey (MCBS) for the years 2000 to 2003. Among the 571 Medicare beneficiaries with PD ≥65 years of age, the annual prevalence of antiparkinson medication use was 58.2%, and levodopa was used by 85.5% of these subjects. Groups found to be less likely to use medication included those who were ≥85 years of age (OR 0.57; $P<0.01$) and those with dementia (OR 0.62; $P<0.001$). Those who were more likely to be on medication included patients who were educated beyond high school (OR 1.51; $P<0.05$), those with medication prescription coverage (OR 1.50; $P<0.01$), and those who were institutionalized (HR 1.78; $P<0.01$).

Although the authors acknowledge that medication use in the absence of significant disability remains controversial, approximately 80% of the subjects in this sample had moderate or greater disability.

Commentary:
Nabila Dahodwala, MD
Assistant Professor of Neurology
University of Pennsylvania
Philadelphia, Pennsylvania

This study provides a bird's-eye view of national patterns of treatment for PD. The fact that 42% of patients were not receiving any type of medication raises concern. However, I think this is somewhat difficult to interpret without more context, particularly without knowing the severity of PD. Some of the sociodemographic and clinical factors that were associated with medication use make intuitive sense. For instance, we would anticipate greater medication use among institutionalized patients and lower medication use among patients without prescription coverage. It is important to note that the study data were collected from 2000 to 2003 and may not reflect several changes in healthcare reimbursement—particularly expansion of prescription coverage for patients on Medicare—that have occurred since that time. The reduced use of PD medications in patients with a low level of education is a particularly concerning finding. This may reflect our failure to explain the benefits of therapy to individuals with low health literacy.

We cannot assume that all of those who were not treated in this study would benefit from medication. One reason for a wide variability in PD care in the United States may be the lack of clear guidelines on which subgroups of patients would most benefit from treatment. The information from this study provides the first step in the identification of potential problems in PD care in clinical practice. Now, we need to understand how these differences in care may affect health outcomes, such as disability and quality of life. ■

Rasagiline protects against alpha-synuclein induced sensitivity to oxidative stress in dopaminergic cells.

First Author and Institution:
KY Chau, MD, Institute of Neurology, London, United Kingdom.

Citation:
Neurochemistry International. 2010;57:525-529.

Objective:
Identify molecular mechanisms that confer rasagiline with neuroprotective effects.

Type of Study:
A model of nigral toxicity in a dopaminergic cell line.

Result:
Rasagiline protected against dopaminergic cell death induced by oxidative stress in the context of alpha-synuclein overexpression. Other favorable changes support a neuroprotective effect.

Conclusion:
The mechanisms of neuroprotection observed in this model provide a possible explanation for disease-modifying effects of rasagiline suggested by recent Parkinson's disease (PD) trials.

The loss of nigrostriatal dopaminergic neurons is widely considered to be a key event in the progress of PD. Several treatments, such as monoamine oxidase (MAO)-B inhibitors, have been suggested to have disease-modifying properties stemming from neuroprotection. However, the precise mechanisms of neuroprotection are unclear.

In this study, the dopaminergic cell line SHSY5Y that was overexpressing wild-type or mutant A53T alpha-synuclein was subjected to free radical-mediated toxicity (via paraquat exposure) in the absence or presence of the MAO-B inhibitor rasagiline. In addition to comparing rates of cell death, cell cultures were evaluated for features associated with cell death pathways, including caspase-3 activity, mitochondrial membrane potential, and intracellular glutathione content (which is associated with oxidative stress management).

In the presence of rasagiline, SHSY5Y cell death induced by overexpression of wild-type or A53T mutant alpha-synuclein and paraquat was reduced. There was an associated reduction in caspase-3 activity and in superoxide generation, and a trend for less compromise of mitochondrial membrane potential. Cellular glutathione levels increased in the presence of rasagiline.

This study confirms a protective effect of rasagiline against free radical toxicity and supports a possible neuroprotective effect through pathways determined in these experiments.

Commentary:
Claire Henchcliffe, MD, DPhil
Associate Professor of Neurology
Weill Cornell Medical Center
New York, New York

Recent intriguing data from large delayed-start design clinical trials, such as ADAGIO (Olanow et al. N Engl J Med. *2009;361:1268-1278), suggest that rasagiline may have a disease-modifying effect in PD, and may slow progression of PD symptoms. Presently, there is no direct means of demonstrating neuroprotection (reducing neuronal cell loss) in vivo in PD, meaning that we must rely on experimental studies in vitro, like this by Chau et al., to precisely determine mechanisms of action that might account for such an effect. A particular strength of this model system is that it attempts to recapitulate PD pathogenesis as a complex interplay of genetic and environmental factors. Increased or mutant alpha-synuclein expression is a well-established risk for PD, and recent epidemiological evidence has demonstrated that paraquat, presumably through increasing oxidative stress, also increases PD risk (Tanner et al.* Arch Neurol. *2009;66:1106-1113).*

This series of experiments adds to our understanding of which basic cellular processes are affected by rasagiline, and it is compelling that positive effects are measured at several key steps associated with programmed cell death, such as caspase-3 activity. Rasagiline's effect on glutathione is particularly interesting, given studies reporting lower glutathione levels in PD substantia nigra, and as yet no proven therapy to reverse this deficiency. The study is undoubtedly well performed, but a key question is this: How relevant are neuroblastoma-derived SHSY5Y cells to dopaminergic cells of the aged substantia nigra? In vivo studies in animal models may generate more compelling evidence, and intensifying efforts in biomarker development will aim to improve methodology able to demonstrate neuroprotection in PD. ■

Mild cognitive impairment in Parkinson disease: A multicenter pooled analysis.

First Author and Institution:
Dag Aarsland, MD, Stavanger University Hospital, Stavanger, Norway.

Citation:
Neurology. 2010;75:1062-1069.

Objective:
Evaluate mild cognitive impairment in a large, multicenter cohort of nondemented patients with Parkinson's disease (PD).

Type of Study:
Pooled data from centers collecting cognitive information on patients with PD.

Result:
Using standardized criteria, mild cognitive impairment was identified in 26% of patients with PD; the most common deficit was in memory, followed by visuospatial and attention impairments.

Conclusion:
In patients with PD without dementia, a range of cognitive deficits, particularly memory impairment, is common. Studies of interventions may be appropriate.

Dementia is a common complication of late-stage PD, but the frequency of mild cognitive deficits in patients with PD without dementia has not been well quantified. One obstacle has been the lack of standardized definitions.

In this study, a single definition of mild cognitive impairment was employed in a large, pooled, multicenter cohort of patients with PD without dementia. Although not all centers employed the same tools to evaluate cognitive decline, adverse changes in three domains of cognitive function were evaluated: 1) memory; 2) attention and executive function; and 3) visuospatial capacity. The definition of impairment was a 1.5 standard deviation below the average for controls adjusted through multivariate analysis for confounding factors, such as education and age.

Among the 1,346 nondemented patients with PD evaluated, 25.8% were classified as having mild cognitive impairment based on the definition employed in this study. The most common deficit was in memory (13.3%), followed by visuospatial impairment (11%). Impairment in attention/executive function was observed in 10.1%. Twenty percent of subjects had only one impairment, but 5.4% of the study group had two and 0.9% had all three. When those with and without mild cognitive impairment were compared, impairment was associated with older age overall and older age at disease onset, as well as more severe motor symptoms, more advanced disease stage, depression, and lower use of dopamine agonists.

This study confirms that mild cognitive impairment is common in nondemented patients with PD, and it suggests that it may be appropriate to pay more attention to this phenomenon. Routine assessment of cognitive impairment in early stages of disease may provide valuable baseline information in evaluating the subsequent course.

Commentary:

Andrew Siderowf, MD
Associate Professor of Neurology
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Philadelphia, Pennsylvania

This is an impressive effort to pool disparate data across treatment centers to derive a reasonable estimate of the frequency of mild cognitive impairment in PD. Based on their estimate that up to 25% of patients with PD have some degree of mild cognitive impairment, these researchers draw attention to a crucial problem and provide the stimulus for further refining how to reliably measure cognitive loss in the clinical setting.

Although there are no established therapies for mild cognitive impairment in PD, patients with mild cognitive impairments may benefit from counseling, lifestyle modifications, and possibly pharmacological treatments with cholinesterase inhibitors, which are useful for Parkinson dementia. Formal studies to treat mild cognitive impairment in patients with PD may also be possible if the dimensions of this problem are better understood.

In the effort to understand mild cognitive impairment in PD, there are a variety of important questions to address, particularly whether these patients are at greater risk for the dementia that occurs in late-stage disease. By bringing together the mild cognitive impairment prevalence studies to date, this paper underscores the evidence that this is a potentially important complication of PD while identifying issues for the prospective studies needed to evaluate how early recognition of mild cognitive impairment might improve patient care. ■

The course of olfactory deficits in patients with Parkinson's disease – A study based on psychophysical and electrophysiological measures.

First Author and Institution:
Thomas Meusel, MD, University Hospital Basel, Basel, Switzerland.

Citation:
Neuroscience Letters. 2010;486:166-170.

Objective:
Evaluate changes in olfactory function over time in patients with Parkinson's disease (PD).

Type of Study:
Prospective study conducted at two time points 5 years apart.

Result:
There was a significant reduction in mean olfactory function over the 5 years of study, but considerable variability within the study group, with some patients actually improving.

Conclusion:
Olfactory function in patients with PD is not static, but fluctuates over time. These fluctuations do not appear to be associated with the course of disease.

Olfactory abnormalities are extremely common in patients with PD, but their significance as a marker of PD is unknown. Although some cross-sectional studies have suggested that olfactory dysfunction remains stable, fewer studies have evaluated olfactory function over time in a single population.

In this study, olfactory function was evaluated in 27 patients with PD using olfactory event-related potentials (OERPs) using an electroencephalogram (EEG) recorded when the patients were stimulated with different odors and with psychophysical tests, such as non-verbal smelling discrimination examinations or multiple choice odor identification tests. The same tests were repeated 5 years later.

Only 19 patients were available for retesting. At baseline, a single patient was normosmic, 14 were hyposmic, and four were anosmic according to psychophysiological tests. At 5 years, one patient was normosmic, nine were hyposmic, and eight were anosmic. There was a mean reduction overall in olfactory function. Three of 19 patients had OERPs at baseline, which were no longer seen at follow-up. There were, however, detectable OERPs at 5 years in three other patients. No correlation was observed between changes in olfactory function and disease status over the time course of the study.

Despite the mean reduction in olfactory function, which may reflect the aging process, there was substantial individual variability observed in this small study.

Commentary:

James F. Morley MD, PhD
Parkinson's Disease Research Education and Clinical Center
Philadelphia VA Medical Center
Department of Neurology
University of Pennsylvania
Philadelphia, Pennsylvania

Hyposmia, a potentially important biomarker for PD progression, has been thought to be constant over the course of illness despite little direct study of olfactory performance over time. Among the strengths of this study are the longitudinal design and 5-year period of follow-up. Additionally, the authors used both psychophysical tests and electrophysiological analysis in the form of OERPs.

Mean psychophysical test scores worsened during the 5-year period, suggesting progression of olfactory dysfunction. However, the change was driven by large declines in only a few subjects. At the individual level, changes tended to be modest and some subjects even showed improvement. All patients with detectable OERPs at baseline had lost them at 5 years, but three subjects with absent responses on initial testing had "regained" them at follow-up. This could reflect the inherent variability of tests superimposed on a relatively static process. The authors did attempt to evaluate the relationship between olfactory function and other clinical changes, such as progression of motor symptoms. However, subgroup analysis with such a small starting sample, as the authors recognize, is difficult to interpret.

Despite these issues, this report challenges the widely held belief that hyposmia in PD is static, but at the same time raises considerable doubt that olfaction might ever be a reliable marker of disease progression. As the authors indicate, larger studies would be needed in the future to address this important issue. ■

Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: A prospective study.

First Author and Institution:
Alex Iranzo, MD, Hospital Clinic de Barcelona, Barcelona, Spain.

Citation:
Lancet Neurology. 2010;9:1070-1077.

Objective:
Predict neurodegenerative diseases in patients with idiopathic rapid-eye-movement sleep behavior disorder (IRBD).

Type of Study:
Prospective evaluation with 2.5 years of follow-up.

Result:
In patients with IRBD sleep behavior disorder, only those with abnormal neuroimaging have progressed to a neurodegenerative disease in follow-up so far.

Conclusion:
Specific neuroimaging features may be valuable for detecting the risk of neurodegenerative disease among individuals with clinical features that suggest increased risk.

The ability to detect Parkinson's disease (PD) or other neurodegenerative disorders before classical features develop may have numerous advantages, including earlier initiation of treatment. Although it has been previously observed that subsequent development of PD or other synucleinopathies stemming from substantia nigra dysfunction is common in patients with IRBD, there is no method for determining who will or will not progress to a neurodegenerative disorder.

In this prospective study, a variety of neuroimaging studies, such as transcranial sonography (TCS) and striatal dopamine function on SPECT, were performed in 43 patients with well-documented IRBD, as well as in healthy controls. After the baseline testing, the participants with IRBD were followed every 3 to 9 months with a battery of sleep, cognitive, and motor function assessments. More detailed neurological function studies were conducted if symptoms consistent with synucleinopathies developed.

At the baseline examination, several abnormalities typical of neurodegenerative disease, particularly reduced ^{123}I-FP-CIT binding on SPECT and tracer uptake reduction on TCS, were found more frequently in the subjects with IRBD relative to the controls. After a median of 2.5 years of follow-up, no patient with IRBD but without an imaging abnormality developed a neurodegenerative disorder. In contrast, eight of the 27 (30%) patients with IRBD who did have an abnormality have developed a neurodegenerative disease so far. These include five with PD, two with Lewy body dementia, and one with multiple system atrophy.

In IRBD, ^{123}I-FP-CIT SPECT and TCS may be useful for identifying patients with a high risk of converting to a neurodegenerative disease even over a relatively short term, and these patients may comprise a group in which to evaluate neuroprotective agents.

Commentary:

Ron Postuma, MD
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Montreal, Canada

An association between IRBD and the risk of PD and other neurodegenerative disorders has been demonstrated in previous studies, but the strength of this study is its prospective design and the effort made to identify specific predictors on imaging. There was a substantial conversion rate over a relatively short follow-up period, and it is reasonable to assume that more conversions will occur as follow-up continues.

Although no specific imaging abnormality was a reliable predictor of conversion on its own, the sensitivity and specificity improved when several changes were considered together. Further follow-up will be important for understanding whether the abnormalities on imaging can predict disease even when it is 5 or 10 years away. Although predicting the risk of PD may be modestly helpful now, this work will be of critical importance if effective neuroprotective therapies become available to change the course of disease. IRBD is a relatively uncommon condition, but this study can be understood within a larger effort to develop screening tools for patients with other potential signs of neurodegenerative diseases, such as changes in olfactory function, that might improve opportunities to detect PD at a subclinical stage. ■

A 12-year population-based study of psychosis in Parkinson disease.

First Author and Institution:
Elin B. Forsaa, MD, Stavanger University Hospital, Stavanger, Norway.

Citation:
Archives of Neurology. 2010;67:996-1001.

Objective:
Identify prevalence and risk factors for psychosis in Parkinson's disease (PD).

Type of Study:
Prospective, longitudinal, cohort study.

Result:
The majority of patients with PD develop psychosis over the long term; the risk increases in patients with PD onset at older age, probable rapid-eye movement (REM) sleep behavior disorder, and use of higher levodopa doses.

Conclusion:
Psychosis—which is associated with a more severe course of PD, including greater disability and increased likelihood of dementia—is common in PD and an appropriate target for therapy trials.

The association between psychosis and PD is well recognized, but estimates of the exact incidence, derived primarily from cross-sectional studies, have ranged broadly.

In this longitudinal cohort study, a part of the population-based PD prevalence study known as the Stavanger Parkinson Project being conducted in a region of 220,000 inhabitants, 230 individuals diagnosed with PD were followed for 12 years and evaluated for a variety of motor and nonmotor features. For this set of Stavanger Project data, the focus was on the prevalence and risk factors for psychosis.

Over the 12 years of follow-up, a total of 59.5% of patients developed PD-associated psychosis (PDP; e.g., hallucinations or delusions) based on the Unified Parkinson's Disease Rating Scale thought disorder (UPDRS-TD) item 2. The incidence of new PDP (after baseline) was 42%. This translated into an overall incidence rate of 79.7 per 1,000 person-years. The predictors of PDP at baseline were a probable diagnosis of REM sleep behavior disorder, an older age (linear progression in risk), and need for higher doses of levodopa.

These findings suggest PDP is more common than many previous estimates. The association between higher doses of levodopa and the presence of REM sleep behavior disorder focuses attention on the dopaminergic pathway in the pathophysiology of this complication.

Commentary:
Hubert H. Fernandez, MD
Head, Movement Disorders
Center for Neurological Restoration
Cleveland Clinic
Cleveland, Ohio

There are not many well-conducted studies that follow patients for 10 or more years in PD, most especially in PDP. The evidence that more than half of patients with PD followed long term will develop psychosis is helpful to know. This is on the upper end of the estimates that have been published previously, and it may even be a conservative estimate based on the methodology of the study. For example, the UPDRS-TD subscale used to diagnose psychosis in this study is not the most sensitive test. At best, it is a single-item question in Part I of the UPDRS that is used as a screening tool. There is also no mention that antipsychotic therapies were taken into consideration, so some patients may not have met the criteria for psychosis simply because their symptoms were controlled with medications.

This study confirms several associations that we already suspected, such as increased age and duration of disease, and included the fact that patients on relatively high doses of levodopa appear to be at a higher relative risk of developing psychosis. One of the most intriguing findings is that probable REM sleep behavior disorder is a predictor of future psychosis. This may provide some clues about links between PD and Lewy body dementia, which is also associated with REM sleep behavior disorder.

The take-home message for clinicians is that psychosis is a much more common problem in PD than we currently realize, and it often predicts a more malignant disease course. Articles such as this underscore the need for better treatment strategies for this complication. ■

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