Volume 2, Number 2
Summer 2009

Parkinson's Disease Monitor & Commentary

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

From the editor...


Andrew D. Siderowf, MD

In this issue of *Parkinson's Disease Monitor and Commentary*, we continue to review recent high-impact publications. Dr. Laura Marsh of Johns Hopkins University uses a study that evaluated apathy as a prognostic indicator for parkinsonism in Alzheimer's disease to point out the frequency with which the problem of patient apathy is overlooked. She appropriately warns how this issue can confound the recognition of cognitive decline or even the accurate evaluation of movement symptoms.

Dr. Matthew Stern reviews a study on the risk of developing PD for patients with REM sleep behavior disorder, relating it to his own studies of hyposomia. Another study looks at hyposomia in patients with suspected PD but without evidence of dopaminergic deficits (SWEDDs).

Of course, not everything in this issue is for immediate clinical application. Among studies looking at issues more relevant to basic science, Dr. Vivianna Van Deerlin of the University of Pennsylvania uses her commentary on a genetic linkage study in PD to quickly explain potential false leads in this avenue of research.

By gathering perspectives on specific areas of research in which our commentators are active, we are often able not only to put a particular study into context, but also provide at least some insight about where this area of inquiry is headed. We intentionally look for a mix of studies with immediate clinical relevance and those that give a flavor of current areas of research. We hope the format can help clinicians stay in touch with on-going research initiatives. Suggestions are always welcome. Please feel free to reach me at info@delmedgroup.com.

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This publication has been supported by an educational grant from Teva Neuroscience.

In This Issue:

PD Monitor & Commentary

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Faculty Disclosure:
Dr. Siderowf has received honoraria from Boehringer-Ingelheim, Schwarz Pharma, and Teva Neuroscience.

Publishing Information

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Ridgewood, NJ 07450
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Apathy predicts more severe parkinsonism in Alzheimer's disease.

First Author and Institution:
Sergio Starkstein, MD, PhD, University of Western Australia, Fremantle Hospital, Fremantle, Australia.

Citation:
American Journal of Geriatric Psychiatry. 2009;17:291-298.

Objective:
To evaluate the chronological sequence of apathy and parkinsonism in Alzheimer's disease (AD).

Type of Study:
Longitudinal evaluation of consecutive patients.

Result:
Unrelated to other variables, patients with apathy at baseline were significantly more likely to develop parkinsonism symptoms than patients without apathy.

Conclusion:
Apathy may be an early sign of a more severe neurological disorder.

Parkinsonian symptoms are a frequent complication of AD. Apathy is also a common complication of AD and other neurological disorders, including Parkinson's disease (PD).

In this study, 169 patients with probable AD were followed longitudinally to determine the chronology of apathy and PD in AD, and to evaluate the influence of these complications on the course of AD. The Unified Parkinson's Disease Rating Scale (UPDRS) was among the objective tests administered.

AD patients with apathy at baseline or who developed apathy over the course of a follow-up assessment of 1-4 years had a significant increase in parkinsonism symptoms at the end of follow-up relative to those who did not develop apathy. The positive correlation between apathy and greater parkinsonism was independent of age, gender, presence of depression, severity of cognitive deficits, or use of psychotropic medications.

Commentary:

Laura Marsh, MD
Director, Clinical Research Program
Morris K. Udall Parkinson's Disease Research Center
Johns Hopkins University School of Medicine
Baltimore, Maryland

Apathy is a common complication of many neurologic disorders, including both AD and PD. As a major burden for patients and caretakers, apathy is also a neglected target of management. This may be even more important if, as this study suggests, apathy predicts a more severe disease course.

One of the strengths and unique features of this study was that it evaluated apathy in relationship to parkinsonism in AD patients with a longitudinal design. Relative to cross-sectional analyses, which limit findings to the time of evaluation, a longitudinal analysis permits an assessment of the impact of a variable such as apathy to be considered for its impact on prognosis. The authors also deserve credit for differentiating apathy from depression as well as from cognitive deficits. Apathy and depression are easily confused, but are very different problems that are likely to require different interventions.

There were several problems with this study. For example, the authors employed UPDRS in an AD population, but a variety of AD symptoms, including poor comprehension of instructions, might yield poor UPDRS scores independent of parkinsonism. In addition, there seems to be an underlying assumption of shared pathology for these motor and mood deficits, but this may not be justified. For example, the rigidity that is associated with AD may have a different pathologic basis than the rigidity observed in PD. However, it is important to better understand the impact of apathy on neurologic diseases, including PD and AD, because of its potential to lead to better management. ■

Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder.

First Author and Institution:
Ronald B. Postuma, MD, Montreal General Hospital, Montreal, Quebec, Canada.

Citation:
Neurology. 2009;72:1296-1300.

Objective:
Quantify the risk of developing a neurodegenerative disorder in patients with REM sleep behavior disorder (RBD).

Type of Study:
Retrospective follow-up of consecutive patients.

Result:
Based on 93 patients with idiopathic RBD followed for up to 12 years, the estimated risk of a neurodegenerative disorder is 18% after 5 years, 41% after 10 years, and 52% after 12 years.

Conclusion:
RBD is a strong predictor of the development of neurodegenerative disorders, with Parkinson's disease (PD) and Lewy body dementia being the most common associated conditions.

Although it has been observed previously that RBD often precedes the development of neurodegenerative disorders, recent data suggest that the link may be α-synuclein deposition, which is also implicated in the pathogenesis of PD and Lewy body dementia. This study was undertaken to better quantify the risk of neurodegenerative diseases in patients who first present with RBD.

In this study, all patients with a diagnosis of RBD evaluated at the sleep disorders laboratory in a single institution since 1989 were re-evaluated. The mean age of the participants was 65.4 years. Men represented 80% of the study population.

Of the 93 evaluable patients, 26 developed a neurodegenerative disorder. Of these, 14 developed PD, seven developed Lewy body dementia, four developed dementia consistent with Alzheimer's disease, and one patient developed multiple system atrophy. When a life table survival curve was created, the estimated 5-year risk of developing a neurodegenerative disease in this population was an estimated 17.7% at five years, 40.6% at 10 years, and 52.4% at 12 years. There was no difference in the duration of RBD among those who did or did not develop a neurodegenerative disease.

The results are consistent with past studies and may be useful for counseling patients with RBD and, eventually, pursuing potential markers of early disease.

Commentary:

Matthew B. Stern, MD
Professor of Neurology
University of Pennsylvania
Philadelphia, Pennsylvania

The relationship between idiopathic RBD and neurogenerative diseases, particularly PD, is fascinating for what it may reveal about a common pathophysiology. Recently, we and others have become interested in impaired olfaction as a predictor of both RBD and PD. Although only a proportion of patients with olfactory dysfunction will eventually develop PD or a related disorder, we hope to refine risk factor assessment so that patients can be identified earlier in the course of their disease when pathology is more limited and disease-modifying therapies are likely to have a greater impact.

In the large-scale, multicenter Parkinson's At-Risk Study, we have already demonstrated that RBD is associated with a greater likelihood of hyposomia and that shared risk factors including RBD, constipation, depression, and anxiety increase the likelihood of hyposmia. Studies are now underway to determine whether these same risk factors not only increase the likelihood of hyposmia, but are also associated with altered dopamine transporter binding by SPECT imaging, a more precise predictor of impending PD.

This study clearly demonstrates that RBD is an early risk factor for neurodegeneration. Such early signals of disease suggest that it may be feasible to identify a population that is at sufficient risk of developing a neurodegenerative disease to design a clinical trial of disease prevention. While this will depend upon having the right therapeutic interventions as well as a paradigm that minimizes false positives and false negatives, this line of research is clearly paving the way for the future of neurodegenerative disease management, in which early detection, intervention, and even prevention will be achievable. ■

Olfaction in patients with suspected Parkinsonism and scans without evidence of dopaminergic deficit (SWEDDs).

First Author and Institution:
Laura Silveira-Moriyama, MD, UCL Institute of Neurology, London, United Kingdom.

Citation:
Journal of Neurology, Neurosurgery, and Psychiatry. 2009; epub ahead of print.

Objective:
Evaluate whether smell tests can help stratify patients with probable Parkinson's disease (PD) for confirmatory imaging.

Type of Study:
Comparison of olfactory function in patients with SWEDDs and several types of controls.

Result:
Smell test scores were in the range defined as a high probability of PD in 23.8% of SWEDD patients versus 85.3% of patients with PD, making it potentially useful for PD screening.

Conclusion:
According to these data, a normal smell test in a patient with suspected PD triples the likelihood of normal dopamine imaging and a diagnosis other than PD.

Approximately 10% of patients with a clinical diagnosis of early PD do not show abnormalities on a dopamine transporter screen with SPECT or PET imaging. Testing patients suspected of PD for hyposomia, which occurs in 80% to 100% of patients with PD, may provide a useful tool for identifying patients with a high probability of PD.

In this study, olfactory function was evaluated in 21 patients suspected of PD but who had scans without evidence of dopaminergic deficiency (the SWEDDs group), 26 patients with essential tremor, 16 patients with a diagnosis of idiopathic adult-onset dystonia, 191 non-demented patients with PD, and 136 controls. The evaluation was performed with the University of Pennsylvania Smell Identification Test (UPSIT), which is a 40-item validated questionnaire for odor identification. Low scores indicate impaired ability to smell.

The mean UPSIT scores of patients with SWEDDs were greater than in the PD group, but not significantly different from controls, essential tremor patients, and adult-onset dystonia patients. While 85.3% of patients with PD had impaired olfactory function on the UPSIT, a positive smell test was obtained in only 23.8% of patients with SWEDDs. According to the authors, a low UPSIT score, indicating a high probability for PD, would be accurate in 97% of PD patients. Conversely, based on the patients with SWEDDs, they calculated that a high UPSIT score, indicating a low probability of PD, increased the likelihood of normal imaging by three fold.

The authors concede that a negative UPSIT evaluation does not eliminate the possibility of PD in a patient with SWEDDs, but that this result in the context of a poor response to levodopa or the absence of progressive severity of symptoms strongly suggests an alternative diagnosis.

Commentary:

Danna Jennings, MD
Clinical Research Director
Institute for Neurodegenerative Disorders
New Haven, Connecticut

There is a great deal of interest in developing effective, simple, and non-invasive screening tools for PD. Olfactory testing is one of the areas that is attracting a great deal of interest. This and other studies have suggested that impaired olfaction has very good sensitivity. However, the presence or absence of olfactory deficits is not very specific, so smell testing does not appear to be useful as an isolated method of evaluation. There are a variety of ways that specificity might be improved, including combining it with other clinical characteristics, such as presence of REM behavior disorder or early autonomic symptoms.

In making a case for olfactory screening, this study had some limitations. Indicative of some methodological weaknesses, one problem was that only 29 of the patients with PD had undergone dopaminergic deficiency imaging, which limits the strength of the important comparison made between these patients as an index of PD relative to those with SWEDDs.

Olfaction identification is being evaluated as a potential screening tool for PD, but several important questions need to be addressed before smell testing can be incorporated into strategies for diagnosis. ■

Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation. The COMPARE trial.

First Author and Institution:
Michael S. Okun, MD, University of Florida, Gainesville, Florida.

Citation:
Annals of Neurology. 2009; epub ahead of print.

Objective:
Compare cognitive and mood effects of two techniques of brain stimulation in patients with Parkinson's disease (PD).

Type of Study:
Prospective, blinded, randomized clinical study.

Result:
No differences overall were detected in executive function or acute emotional state when comparing deep brain stimulation (DBS) to the subthalamic nucleus (STN) versus the globus pallidus interna (GPi).

Conclusion:
The specific technique may not be important to the relative risk of developing cognitive or mood disturbances after DBS, but lead placement may have an effect.

Mood disorders and cognitive impairment have been described after DBS, but the risk of these complications after DBS of the STN relative to DBS of the GPi is unknown.

In this study, 52 patients with PD who were candidates for DBS were randomized to receive unilateral DBS to the STN or the GPi. Mood was measured with the Visual Analog Mood Scale (VAMS), while cognition was evaluated with a verbal fluency test. Baseline measures were compared to evaluations conducted 7 months after completion of DBS. At both timepoints, patients were evaluated off medications.

Of the 45 patients who completed the protocol and were available for evaluation, 22 underwent the STN technique and 23 received DBS to the GPi. At baseline, there were no differences in mood, cognition, or disability as assessed with the Unified Parkinson's Disease Rating Scale (UPDRS), although patients undergoing STN DBS had greater disease severity. When evaluated after DBS, there were no clear, overall changes in either mood or cognition for the entire sample. In addition, there were no clear differences between those who underwent STN versus GPi DBS in mood, cognition, or motor outcomes.

Commentary:

Daniel Weintraub, MD
Assistant Professor of Psychiatry and Neurology
University of Pennsylvania
Philadelphia, Pennsylvania

One of the major strengths of this study is that it randomized patients to two different types of DBS, permitting an uncommon opportunity to evaluate GPi and STN DBS side by side. Using a blinded evaluator to assess outcomes, the study also was designed to permit the effect of different lead locations (optimal motor placement versus ventral versus dorsal) to be evaluated, and to isolate the effects of DBS versus medication. The limitations of the study are that it was conducted at a single site with a relatively small number of evaluable patients. The study also employed unilateral DBS even though most DBS is performed bilaterally.

Although there were no clear effects of DBS surgery overall or differences between the two types of DBS surgeries on mood or cognition outcomes as measured by the investigators, the tools for evaluating patients were limited. For example, the mood scale used assesses instantaneous emotions and was administered once during follow-up, providing a better snapshot of the acute emotional state at the time of the evaluation than a perspective on sustained mood. Similarly, one conclusion was that there were no overall differences in cognition between the surgical techniques, but only one type of cognitive test, verbal fluency, was employed. In addition, patients post-surgery were evaluated off medications to better identify the effect of DBS, but in clinical practice most DBS patients remain on PD medications. Thus, the study is important for its clinical relevance, the preliminary results suggesting that DBS surgery and stimulation are well tolerated in terms of mood and cognition, and the questions that it raises for future research, but the clinical applicability and generalizability of the results are limited. ■

There were no clear differences between those who underwent STN versus GPi DBS in mood, cognition, or motor outcomes.

Spinal cord stimulation restores locomotion in animal models of Parkinson's disease.

First Author and Institution:
Romulo Fuentes, MD, Duke University Medical Center, Durham, North Carolina.

Citation:
Science. 2009;323:1578-1582.

Objective:
Test electrical stimulation of the spinal cord as a substitute for deep brain stimulation (DBS) in a Parkinson's disease (PD) model.

Type of Study:
Animal study.

Result:
Electrical stimulation of the dorsal spinal column provides functional recovery in an animal model similar to that achieved with human DBS. When given with levodopa (L-dopa), it reduces the dose requirement.

Conclusion:
Dorsal column stimulation (DCS) may be a less invasive alternative to DBS for the treatment of PD.

DBS is a technically demanding surgery and a highly invasive procedure in a patient population that may already be frail. Spinal cord stimulation has shown promise in the treatment of several neurologic diseases, including pain, and is relatively simple to perform. In this series of experiments, DCS was administered by epidural implanted bipolar electrodes in animal models of PD and in combination with L-dopa in mouse PD models.

In all models and conditions, DCS restored locomotion capability. After DCS, activity in the primary motor cortex and the dorsolateral striatum mimicked that observed during spontaneous initiation of locomotion in normal mice. The authors speculated that this effect may be due to motor-related brain area shifts into a state permitting initiation of movement.

On the basis of these animal studies, the authors conclude that DCS deserves to be pursued as a possible therapy for human PD and as an alternative to DBS.

Commentary:

Michael S. Okun, MD
Departments of Neurology and Neurosurgery
University of Florida
Gainesville, Florida

This study of DCS in PD is interesting for what it might tell us about the descending basal ganglia pathways. Studies in PD are generally confined to modifying brain activity, particularly pathways in the supra-spinal basal ganglia. There are, however, many descending basal ganglia connections, and it is not unreasonable to speculate on their usefulness for improvement in gait and balance function. One recently published and important PD DBS study was of PPN DBS for the treatment of L-dopa-unresponsive gait disorder. The improvement in locomotion in animal models working on potential descending basal ganglia pathways may therefore deserve more attention, and it is intriguing that the authors chose the spinal cord as a target.

The authors suggest that DCS may provide an alternative to human DBS, but this is not consistent with their published results or with the animal models they employed in their experiments. The challenge and the greatest current need in PD are therapies for individual patients who have symptoms (e.g., gait, balance, etc.) that are no longer responsive to pharmacological options. The animal models employed in this study were unfortunately L-dopa responsive, and therefore they may not parallel what is seen in the human condition—particularly later in the disease course. Although safer and more effective alternatives to DBS are needed, the extrapolation that the improvement in locomotion observed with DCS in these animal models may be relevant to patients unresponsive to current pharmacological therapies is not warranted. There is no animal model that recapitulates L-dopa-resistant PD symptoms, so the conclusions in this study may have been too expansive.

Although DCS has not been extensively evaluated in the PD population, it is not a new technology. Despite evaluation in a broad array of neurological disorders, its most frequent clinical application has been in the treatment of pain. The truth behind the notion that DCS may help L-dopa-unresponsive gait and balance dysfunction in the human is unknown, but it is a testable and potentially important follow-up study. ■

Genome-wide linkage screen in familial Parkinson disease identifies loci on chromosomes 3 and 18.

First Author and Institution:
Xiaoyi Gao, MD, University of Miami Miller School of Medicine, Miami, Florida.

Citation:
American Journal of Human Genetics. 2009;84:499-504.

Objective:
Localize regions of the genome likely to harbor susceptibility loci for Parkinson's disease (PD).

Type of Study:
Genome-wide linkage evaluation in families with multiple members with PD.

Result:
Significant evidence of linkage was found for chromosome 18q11, with weaker linkage for chromosome 3q25.

Conclusion:
The findings increase the likelihood that additional PD susceptibility genes can be identified with targeted candidate gene studies in these regions.

New technology for evaluating the genome is improving the opportunities for detecting genetic susceptibility to common diseases, including PD. In the past, genome-wide scans have identified several regions of interest. In a previous linkage study by the same authors, linkage to PD was implicated for chromosomes 5, 8, 9, 17, and X.

In this study, the authors used single-nucleotide polymorphisms (SNPs) to guide a more sophisticated genome-wide linkage panel to confirm their original results in the 158 families included in the previous study (published in 2001) plus 120 additional families (total 278 families). All were of European non-Hispanic background. Family members without PD represented slightly less than half of the total family members evaluated.

The regions of strongest linkage were identified on chromosome 18q11 and chromosome 3q25. However, the areas of interest identified in the previous study were not reproduced with the more sophisticated testing. When results were stratified to compare newly added families to the original cohort of studies, it was found that the chromosome 3 and 18 regions were stronger in the new cases than in the original cohort.

Although the authors concede that the different results generated by the newly added cohort when compared with the original cohort could represent chance, they argued that locus heterogeneity among the families is a better explanation. Due to the complexity of PD and the likely participation of several types of familial susceptibility, the authors urged future studies employing cautious sample collection and interpretation when looking for candidate disease risk genes.

Commentary:

Vivianna Van Deerlin, MD, PhD
Associate Professor of Pathology and Laboratory Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

This study, which scanned the whole genome rather than specific areas of interest, is the first to associate the 18q11 and 3q25 regions with PD. Although these findings are of interest, the authors had set out to confirm a previous linkage they found using microsatellite marker sets in chromosomes 5, 8, 9, 17, and X. It should be noted that due to the complexity of the genetics, particularly in PD, confidence in a region of interest accumulates with repeated results with different methodologies and in larger and more diverse patient cohorts. If these findings, achieved with the relatively new high-throughput SNP genotyping, hold up, it will still be a first step along a long path. On 18q11, the chromosome with the strongest linkage in this study, there are 90 known genes. The studies that will be needed to identify the specific gene or genes important to PD at this location will not be trivial. It is important to note that the identification of this region was not hypothesis-driven, so the putative mechanism of PD controlled by the genes is unknown. In addition, the potential for the play of chance cannot be ruled out even with a cohort of almost 300 families.

Based on the clinical phenotypes of PD and the genetic studies conducted to date, there are almost certainly multiple pathways of familial susceptibility for PD. This study identifies a new area of interest, but it is one of many. ■

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