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

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From the editor...

The same evidence-based standards of medicine that are expected for trials of new pharmacotherapies should be also be expected of studies of new ways to deliver care. In keeping with that sentiment, in this issue of *PD Monitor & Commentary*, Dr. Samuel Frank of Boston University reviews a controlled study of group visits for patients with Parkinson's disease (PD). Despite promising preliminary research, the study was negative for its primary outcome, but Dr. Frank believes the endpoint may have been too narrow.

ANDREW D. SIDEROWF, MD

This issue also includes studies of how biomarkers may ultimately impact clinical care. Dr. Paul Tuite of the University of Minnesota critiques an article on the potential clinical application of PD biomarkers, while Dr. Danna Jennings of the Institute for Neurodegenerative Disorders in New Haven, Connecticut evaluates an investigation of olfaction and color vision tests to identify early-stage synuclein-mediated neurodegenerative diseases. In the area of therapeutics, Dr. Laura Marsh of the Baylor College of Medicine in Houston reviews a study that looks at the effect of the MAO-B inhibitor rasagiline on cognitive function in patients with PD, and Dr. Fernando Pagan of Georgetown University provides his perspective on a trial of disease progression in young-onset PD. Finally, Dr. Matthew Brodsky of the Oregon Health & Science University evaluates a research initiative that attempts to determine which specific cognitive deficits are most related to visual hallucinations seen in patients with PD dementia.

Next, in the "Q&A" column, I review the latest information on the supplement coenzyme Q10 and whether it is of benefit for patients with PD, while in our new "Controversies" section Dr. Tanya Simuni of Northwestern University presents the pro argument on the question of biomarkers and drug discovery in PD, while Dr. John Morgan of the Medical College of Georgia takes the con position.

We hope the selection of articles in this issue conveys the wide range of efforts underway to improve care or better understand this disease. Please feel free to contact me with suggestions or comments at info@delmedgroup.com.

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NEW: CONTROVERSIES IN PD AND Q&A WITH ANDREW D. SIDEROWF, MD

PDMC

In This Issue

Commentaries

Q&A with Andrew Siderowf, MD

Controversies in PD

John C. Morgan, MD, PhD

Tanya Simuni, MD

The effects of rasagiline on cognitive deficits in Parkinson's disease patients without dementia: a randomized, double-blind, placebo-controlled, multicenter study.

First Author and Institution:

Hasmet A. Hanagasi, MD, Istanbul University, Istanbul, Turkey.

Objective:

Evaluate benefit from rasagiline against cognitive deficits in Parkinson's disease (PD).

Type of Study:

Multicenter, double-blind, placebo-controlled trial.

Result:

Over a period of 3 months, rasagiline was associated with significantly improved test performance in several areas of cognition, including verbal fluency, digit ordering, and attention relative to placebo.

Conclusion:

In non-demented patients with PD with cognitive impairments, rasagiline appears to improve some aspects of cognitive function.

Progressive cognitive impairment, a common feature of PD, can eventually lead to dementia at advanced disease stages. Treatment of mild cognitive impairment at early stages may not only provide an immediate improvement in quality of life but may slow or prevent further cognitive loss. There is a theoretical possibility that drugs that act on central dopaminergic transmission, such as monoamine oxidase type-B (MAO-B) inhibitors, may improve cognition.

In this study, 55 patients who were non-demented but cognitively impaired and taking stable doses of dopaminergic treatment were randomized to receive 1 mg rasagiline per day or placebo. Using validated neuropsychological tests, the cognitive domains of global attention, executive function, memory, and visuospatial function were measured at baseline and at the end of the 12-week study. Enrolled subjects were required to have deficits in at least two of these four cognitive domains. Forty-eight patients completed the study.

When the tests were repeated at the end of the study, there was a significant improvement (P=0.04) in one of the four tests designed to test attention and trends for benefit in two of the others (P=0.058 and P=0.052). For executive function, there was a significant improvement in verbal fluency (P=0.038) and trends for a benefit in semantic verbal fluency (P=0.06) and Stroop spontaneous corrections (P=0.056). There were no significant benefits or trends for benefit in the memory or visuospatial cognitive domains.

The evidence for benefit from rasagiline in aspects of attention and executive functions encourages larger-scale studies, including those designed to determine whether rasagiline slows the rate of cognitive decline.

Commentary:

Laura Marsh, MD
Professor of Psychiatry and Neurology
Baylor College of Medicine
Houston, Texas

For patients with PD, cognitive decline is a major clinical issue for which there are no definitive therapies currently available. Drugs that increase dopaminergic transmission have the potential to improve cognitive function, but there is also a risk of adverse effects.

This well-conducted randomized, double-blind trial provides a modest signal that rasagiline may benefit selective aspects of attention and executive function and encourages further studies. However, certain limitations restrict the scope of its conclusions. One issue for me was that the study did not include assessments of self-reported cognitive function or everyday cognitive functioning (in addition to objective test performance). Whereas rasagiline was associated with significant changes in discrete measures of cognitive function, such additional data would enhance the clinical relevance of the findings. Another concern is that the authors reported several statistical "trends," and these should be interpreted with caution given the study's small sample size. However, it is reassuring that cognitive function did not worsen in the treatment group.

An early intervention for PD that may slow or prevent progressive cognitive loss and also address motor dysfunction is attractive. Rigorous study designs are important because of the complexity of factors that affect cognitive function, such as depression, and the need to assess effects on real-life performance in addition to objective cognitive capacity. ∎

Age-specific progression of nigrostriatal dysfunction in Parkinson's disease.

First Author and Institution:
Raul de la Fuente-Fernández, MD, University of British Columbia, Vancouver, Canada.

Citation:
Ann Neurol. 2011;69:803-810.

Objective:
Evaluate impact of age on nigrostriatal dopamine dysfunction in patients with Parkinson's disease (PD).

Type of Study:
Prospective positron emission tomography (PET) scan study of dopamine markers in patients and controls.

Result:
Nigrostriatal dysfunction progresses more slowly and damage to dopiminergic function is greater before the onset of symptoms in younger patients with PD compared with older patients.

Conclusion:
Slower clinical progression in younger patients may be due to greater adaptive abilities to dopaminergic dysfunction, more resistance to dysfunction, or some combination of these.

Many clinicians have the impression that symptoms progress more slowly in patients who develop PD at a relatively young age when compared to older patients. While there is a variety of evidence suggesting that most of the damage to the nigrostriatal system occurs before the onset of symptoms, it is not clear whether the rate of dopaminergic loss is slower in younger patients.

In this study, 78 patients with PD and 35 healthy controls were enlisted to undergo longitudinal PET studies in which three presynaptic dopamine markers were evaluated over an 8-year period of follow-up. Generating independent information about nigrostriatal function, these markers provided reproducible measurements of vesicular monoamine transporter type, density of the plasma membrane dopamine transporter, and the activity of the enzyme dopa-decarboxylase. The patients with PD, all of whom had a negative family history for PD, were stratified by those with symptom onset before 44 years of age, between 44 and 66 years of age, and after age 66.

On imaging, the clinical progression of PD was slower in the youngest group of patients. When evaluated in the context of PET changes over time (438 PET scans in patients and 279 scans in controls), dopamine markers suggested slower progression and more damage to the nigrostriatal dopamine system relative to symptom expression in younger versus older patients.

Based on these findings, the authors conclude that the slower clinical progression observed in younger patients with PD is due both to a slower neurodegenerative process and to a greater adaptive capacity to compensate for loss of dopamine function.

Commentary:
Fernando Pagan, MD
Co-Director, Movement Disorders Program
Georgetown University Hospital
Washington, DC

This study provides important new information. Although we, like others, have noticed that patients with onset of PD at a young age have slower clinical progression, this is the first time that the observation has been validated and explored with neuroimaging. The use of biomarkers was an interesting and novel approach to seeking an objective basis on which to understand this phenomenon.

Given the expense and difficulty of performing serial PET scanning, I thought the sample size was quite reasonable. One potential criticism is that the investigators did not specifically perform genetic testing. Although they did exclude patients with a family history of PD, a higher percentage of patients with young-onset PD have a genetic predisposition, and it would have been helpful to specifically evaluate whether this differed between the age groups.

The evidence that disease progression is different in younger patients creates an important question: Should treatment strategies be modified for younger versus older age groups? This is not a question that this study was designed to answer, but it creates a framework for designing such studies. Using these types of biomarkers along with clinical observation, it might be possible to determine whether outcomes can be improved by a specific order of therapy, such as starting with an MAO-B inhibitor, L-dopa, or a dopamine agonist. This is an important direction of research. ■

Cognitive correlates of visual hallucinations in dementia associated with Parkinson's disease.

First Author and Institution:
Kolbjorn Bronnick, PhD, MSc, Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger, Norway.

Objective:
Compare the cognitive profile of hallucinating versus non-hallucinating patients with Parkinson's disease dementia (PDD).

Type of Study:
Sub-analysis of previously published multicenter, international EXPRESS study.

Result:
Of a variety of cognitive variables evaluated, a deficit in attentional control was the only one to correlate significantly with visual hallucinations.

Conclusion:
Contrary to the hypothesis that visuospatial cognitive deficits underlie an increased susceptibility to visual hallucinations in patients with PDD, loss of attentional control may have a closer association.

Some 41% to 87% of patients with PDD suffer from visual hallucinations. In this study, 86 patients with PDD and hallucinations were compared to matched patients with PDD but without hallucinations. All patients had participated in the EXPRESS study, which evaluated the efficacy of rivastigmine, a cholinesterase inhibitor, for the treatment of cognitive loss in PD (Emre et al. *N Engl J Med.* 2004;351:2509-2518). A logistic analysis was conducted to identify changes in cognitive function associated with hallucinations. The authors hypothesized that both executive/attentional control and visuospatial functions would be more greatly disturbed in those with hallucinations than those without hallucinations.

The only independent predictor of hallucinations on the regression analysis was worse choice reaction time ($P<0.001$). In a more detailed analysis, response selection was significantly more impaired in those with hallucinations than those without, while there was no difference in the stimulus discrimination measure. The authors describe these results as reinforcing a "top-down" rather than a "bottom-up" disturbance in cognitive processing, meaning that a change in attentional control is likely to be more important than a fundamental defect in visual perception for risk of hallucinations.

The authors suggest these findings encourage a new set of studies with visual stimuli that may help differentiate "top-down" reactions due to disorders of attention from "bottom-up" changes in visual perception as the primary source of hallucinations in patients with PD.

Commentary:
Matthew A. Brodsky, MD
Associate Professor of Neurology
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Portland, Oregon

In clinical practice, hallucinations are commonly observed in patients with PD and cognitive deficits. Both are disturbing complications of advancing disease. Identifying and understanding the relationship between cognitive impairment and hallucinations is potentially useful, but there were a number of methodological problems with this analysis that make the results difficult to interpret. One of these was the failure to provide detailed information about exposure to dopaminergic medications, such as dopamine agonists. Although the study did match patients and controls for levodopa equivalence, there was no information regarding which class of dopaminergic medications study subjects were taking, and this has the potential to influence the risk of visual hallucinations.

It would also have been very helpful to know more details about the nature of the hallucinations, particularly whether they were formed or unformed. Fully formed images are typically more disturbing to patients than, for example, a transient geometric shape, and there may be differences in the precipitating factors for these types of hallucinations. It would also have been helpful for the authors to provide greater speculation about how this information about the relationship between cognitive deficits and risk of visual hallucinations might lead to more effective treatments. For example, the treatment for attentional disorders is different than the treatment for cognitive impairment.

This is an important area of study, but the present article has to be considered an early step in the types of investigations that might eventually provide clinically meaningful guidance for treatment. ■

Olfaction and color vision identify impending neurodegeneration in rapid eye movement sleep behavior disorder.

First Author and Institution:
Ronald B. Postuma, MD, McGill University, Montreal, Canada.

Citation:
Ann Neurol. 2011;69:811-818.

Objective:
Test predictors of neurodegenerative diseases in patients with rapid eye movement (REM) sleep behavior disorder (RBD).

Type of Study:
Prospective cohort study.

Result:
Abnormalities of olfaction and color vision were highly correlated with the subsequent risk of developing neurodegenerative disorders over a follow-up of 5 years.

Conclusion:
The ability of olfaction and color vision abnormalities to identify synuclein-mediated neurodegenerative diseases in early stages may have clinical application.

RBD, which describes exceptional activity such as loud talking or aggressive body movements during the dream phase of sleep, frequently precedes the development of synuclein-mediated neurodegenerative diseases, such as Parkinson's disease (PD) or Lewy body dementia (LBD). In the context of RBD, disturbances in smell and color vision, which are also predictors of synuclein-mediated disorders, have the potential to be preclinical disease markers.

In this study, patients with RBD and no other evidence of neurodegenerative disease were enrolled into a prospective cohort in which olfaction and color vision were tested at baseline and at annual intervals. At the end of 5 years, the results of the olfaction and color vision tests were compared for those who did and did not develop a clinical neurodegenerative disease. Olfaction was evaluated with the University of Pennsylvania Smell Identification Test (UPSIT). Color vision was evaluated with the Farnsworth-Munsell-100-Hue-Test (FM-100).

Of the 62 patients with complete follow-up, 21 developed a neurodegenerative disease and 41 remained disease-free. Of those with disease, 16 had both dementia and symptoms of parkinsonism, four had parkinsonism symptoms only, and one had dementia only. Five-year disease-free survival was 86% in those with normal olfaction and 35% in those with abnormal olfaction (*P*=0.029). Disease-free survival over the same period was 70% for those with normal color vision and 26% for those with impaired vision (*P*=0.009).

These findings support the theory that abnormalities of olfaction and color vision are preclinical signs of synuclein-mediated disorders. Individuals with these abnormalities may be candidates for neuroprotective therapies when or if such agents become available.

Commentary:
Danna Jennings, MD
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This is one of the first studies to look at abnormalities in color vision as well as smell as preclinical markers for synuclein-mediated disorders. The data make an important contribution to the literature, particularly in regard to Lewy body disease, the parkinsonism syndrome for which these preclinical markers appear to be most closely related.

The proportion of conversion to clinical disease was relatively high in this series, with approximately 1/3 of the patients developing a neurodegenerative disorder. A striking 76% of patients who developed neurodegenerative signs were diagnosed with Lewy body disease over a follow-up of 5 years.

While recruitment of individuals with RBD can be difficult, this study enrolled and maintained a reasonable sample size to test these potential markers of preclinical disease. It is important to recognize that this was a highly selective population evaluated in a research setting. The study population was restricted to patients with RBD, and therefore the findings may not be generalizable to other groups. The data, despite the strong associations, should be considered in the context of a research study, and thus, these markers should not necessarily be considered tests to be performed in clinical practice as a means of counseling patients regarding their individual risk for developing PD or related disorders. However, these data do reinforce an important direction of research and they may define a population, as the authors suggest, that might be a candidate for trials of neuroprotective therapies. ■

Group patient visits for Parkinson's disease.

First Author and Institution:

E. Ray Dorsey, MD, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Objective:

Evaluate effect of group visits as a framework for Parkinson's disease (PD) care.

Type of Study:

Randomized allocation of patients and caregivers to group visits or usual care.

Result:

At the end of a 1-year period, quality of life was not improved in those randomized to group care versus usual care, although this method of care was feasible and not worse.

Conclusion:

A small pilot study was unable to reproduce the benefits of group visits associated with other chronic conditions, but the results do not preclude the potential for advantages.

Group patient visits have been shown to be effective for delivering care for some chronic diseases, such as coronary artery disease and diabetes. According to published studies, group visits, which allow for discussion of common clinical issues, have been associated with improved patient satisfaction with care and improved quality of life. This approach has not been formally studied in PD.

In this study, 30 patients with PD and 27 caregivers were enrolled. The patients were randomized to group patient visits, which consisted of 90-minute group meetings led by a physician plus a 10-minute one-on-one meeting, or to usual care, which consisted of a usual one-on-one physician-patient consultation. The primary outcome was to measure feasibility and to compare dropouts, but quality of life and patient satisfaction were also evaluated.

At the end of 12 months, two patients dropped out of the group-care arm and one out of the usual-care arm. There were no significant differences in quality of life between the two groups (P=0.99). There were also no differences in clinical outcomes, patient satisfaction, or caregiver burden. However, the authors suggest that one potential advantage for the 90-minute group visits is that it permitted physicians to evaluate disease characteristics, such as "wearing-off" and motor fluctuations, over a longer period than usual care. Among the participants, eight of 14 patients who received group care preferred that over usual care, while five of 14 patients who received usual care expressed a preference for group visits.

Commentary:

Samuel Frank, MD
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Boston, Massachusetts

Group care is an idea that has been around for some time and has some potential advantages in PD. A large proportion of clinical issues associated with PD are broadly shared. Group visits allow clinicians to deliver common messages to a broader group, and may also provide reassurance to patients that their issue is not unique. Group visits are used already at some centers, but they have not been formally studied in PD, providing little information about the best approach.

> **Group visits allow clinicians to deliver common messages to a broader group, and may also provide reassurance to patients that their issue is not unique.**

In this study, quality of life among patients was one of the endpoints, and in future studies, it might be appropriate to look at efficiency of care and other measures of quality. As the authors of the study point out, it could be useful for physicians to be able to observe patients over a longer period than the usual relatively brief office visit, even if it proves difficult to measure this advantage.

Reimbursement remains an open question in group care, because there is no system in place to obtain reimbursement even if it were possible to demonstrate that this approach is more cost-effective. If larger studies of group care were to be undertaken, an economic analysis would be appropriate in order to convince third-party payers that it deserves reimbursement. ■

Cerebrospinal fluid biomarkers for Parkinson disease diagnosis and progression.

First Author and Institution:

Min Shi, PhD, University of Washington, Seattle, Washington.

Citation:

Ann Neurol. 2011;69:570-580.

Objective:

Evaluate potential biomarkers for diagnostic and prognostic value in Parkinson's disease (PD).

Type of Study:

Quantify biomarker levels in patients with PD relative to healthy and diseased controls.

Result:

In various combinations, the tested biomarkers, which included tau, amyloid beta peptide 1-42, and Flt3 ligand, differentiated patients with PD from controls and correlated well with disease severity.

Conclusion:

The seven biomarkers in this study, all proteins found in the cerebrospinal fluid (CSF), have the potential to be combined in various panels for diagnosis and prognostication in PD.

The early diagnosis of PD is often challenging because of the broad array of disorders that produce similar symptoms. Recently, elevated levels of alpha-synuclein (α-synuclein) and DJ-1 have been associated with neurodegenerative diseases such as PD, but their specificity appears to be limited, and they do not appear to correlate with or predict disease severity.

In this study, five potential biomarkers associated with PD were evaluated alone or in various combinations with and without α-synuclein and DJ-1 for their potential to be employed in diagnostic evaluations of PD and to predict PD severity. These five biomarkers—tau, phosphorylated tau, amyloid beta 1-42 ($A\beta_{1-42}$), Flt3 ligand, and fractalkine—were evaluated with highly sensitive and quantitative assays in the CSF taken from 126 patients with PD, 137 healthy controls, 50 individuals with Alzheimer's disease (AD), and 32 patients with multiple system atrophy (MSA).

The biomarkers alone, in combination with each other or with α-synuclein and DJ-1, were able to differentiate patients with PD from the controls with varying degrees of

sensitivity and specificity. The Flt3 ligand was particularly effective in differentiating PD from MSA, which has clinical overlap with PD. The sensitivity of this biomarker for PD was 99% and the specificity was 95%. Combined, fractalkine and $A\beta_{1-42}$ correlated with PD severity.

The biomarkers evaluated in this study demonstrate substantial promise as diagnostic tools for PD and, possibly, for predicting disease severity. More studies are warranted.

Commentary:

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

This study, which is representative of the current interest in biomarkers for their potential to rapidly and definitively distinguish neurodegenerative diseases, was well performed. The control groups were appropriate, providing helpful information about the relative sensitivity and specificity of the array of markers tested.

Reliable biomarkers for a diagnosis of PD are needed and would be helpful, but there is one obstacle to these measures even if larger studies validate a panel that can be used routinely in clinical care. The obstacle is the requirement of a spinal tap, which may not be accepted by patients or physicians. This is particularly true if serial spinal taps are performed to help determine the disease course clinically or in research studies. Nonetheless, if proven useful, testing biomarkers in the CSF may gain some enthusiastic supporters. Meanwhile, others are searching for less invasive biomarkers by evaluating serum measures or imaging methods, such as single-photon emission tomography, positron emission tomography, or magnetic resonance imaging.

> **The take-home message from this study is that there is progress toward better methods of separating PD from MSA, and, possibly, for better predicting the course of disease.**

All in all, there is not now—and probably will not ever be—a single biomarker that distinguishes PD from other conditions or predicts the course of disease or response to treatment. The take-home message from this study is that there is progress toward better methods of separating PD from MSA, and, possibly, for better predicting the course of disease. ■

Q&A

WITH EDITOR
Andrew D. Siderowf, MD

Question: Should I recommend that my patients take coenzyme Q10?

Answer: For the past decade, patients with Parkinson's disease (PD) have taken high doses of coenzyme Q10 (CoQ) in the hopes that this supplement might slow down the degenerative process. The enthusiasm for CoQ was based on results from a pilot study conducted by the Parkinson Study Group and published in 2002 that suggested that CoQ at a dose of 400 mg three times a day might slow progression of motor disability.[1] Subsequently, several small studies, such as one by Muller et al, failed to show a conclusive benefit for CoQ.[2] To provide a definitive answer about its role in PD, in 2008 the National Institute of Neurological Disorders and Stroke (NINDS) launched a large-scale, randomized, multicenter, placebo-controlled clinical trial of CoQ called the QE3 study.[3]

While all of this data-gathering has been going on, patients with PD have been taking CoQ, often at considerable out-of-pocket expense, waiting for the evidence to come in.

Earlier this year, the data arrived. NINDS announced the results of an interim analysis of the QE3 study showing there was no benefit of CoQ for PD.[4] Even if the trial was conducted to its planned conclusion, there was no realistic possibility, statistically speaking, that the results would change substantially enough to show a benefit for CoQ. Based on this interim analysis, NINDS stopped the trial. Importantly, no safety concerns were raised by the QE3 study. The two doses of CoQ that were tested, 400 mg and 800 mg three times a day, were both safe and well tolerated.

Based on this finding, I have been recommending that my patients stop taking CoQ for PD. However, if patients want to continue taking it for some other perceived health benefit—to prevent cardiovascular disease, for instance—it is not unreasonable. The preliminary results from the QE3 study show that CoQ is safe, even at very high doses. It may not help PD, but it doesn't harm patients.

Where do the results of the QE3 study leave patients who want to do "everything they can" to slow disease progression? The reality is that there is no specific treatment that has been shown to have a neuroprotective effect in PD. There is some evidence for another supplement, creatine, which is currently being tested in a large government-sponsored study.[5] There is also evidence for inhibitors of the enzyme monoamine-oxidase type-B (MAO-B) such as rasagiline, and for vigorous aerobic exercise.[6,7] However, none of this evidence is strong or consistent enough to conclude that a definite neuroprotective effect exists.

Although it is disappointing that CoQ is not neuroprotective, the results of the QE3 study are still useful to patients with PD who now have a basis to stop taking a treatment that is relatively expensive and is not providing a clinical benefit. Meanwhile, the search for disease-modifying treatments for PD goes on.

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Controversies in PD

The Question:
Will biomarkers accelerate drug discovery in PD?

PRO Opinion

Tanya Simuni, MD

Director, Parkinson's Disease and Movement Disorders Center Northwestern University Chicago, Illinois

All biomarker types being studied in PD have advantages and limitations. An ideal disease-trait biomarker should be directly linked to the underlying disease process, have high positive predictive value, and be feasible to ascertain. In all likelihood, a diagnostic biomarker will consist of a battery of tests that will combine a sensitive but not specific screening test followed by a study with higher specificity. Such an approach is being tested in the Parkinson's disease Associated Risk Syndrome (PARS) study that utilizes a smell test as the screening tool in a large cohort of neurologically normal adults followed by DAT SPECT imaging ([^{123}I] β-CIT) and seeks to establish if a combination of these two tests would reliably select the subjects who will phenoconvert to clinical parkinsonian syndrome.[1] The study is ongoing, but the interim data are encouraging and intriguing.

Although investigational, imaging biomarkers are already being utilized in some interventional studies. A recently completed Phase II study of gene delivery of adeno-associated viral vector (AAV2)-glutamic acid decarboxylase (GAD) therapy utilized fluorodeoxyglucose (FDG) PET scans to demonstrate a PD-specific metabolic network as an inclusion criteria for the study.[2] Likewise, the Parkinson Progression Biomarker Initiative (PPMI) now requires PD subjects to undergo DAT SPECT imaging as verification of the presence of presynaptic dopamine deficiency.[3]

Less data exist on the use of biomarkers of disease state as a surrogate measure of disease progression and ultimately efficacy of treatment intervention. Disease-trait (diagnosis) and disease-state (severity) biomarkers might not be the same. Genetic biomarkers will never serve as disease-state biomarkers as they do not change with the disease progression. The same is true for such imaging biomarkers as transcranial sonography of the substantia nigra. Sensitivity of other biomarkers to change remains to be determined. An attempt has been made to use functional imaging (SPECT or PET) as surrogate measures of the impact of treatment interventions on the biological course of the disease in a number of studies of dopamine agonists and levodopa.[4-6] All studies demonstrated dichotomy of the clinical outcome measures pointing in the opposite direction from the results of imaging. The studies raised a lot of debate and the conclusion was made that utilization of functional imaging in PD interventional studies was premature.[7] The conclusion was fully justifiable, but did not eliminate the possibility of utilizing it in the future.

While surrogate measures of efficacy of treatment intervention in PD will become a reality hopefully in the next decade, in order to achieve that goal, first biomarkers of disease progression have to be validated. The largest study aimed to develop such biomarkers, the PPMI, is going on now and the data will be invaluable.[3] The horizon for the biomarker research in PD is challenging but quite optimistic.

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A biomarker (or biological marker) is defined as a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [Biomarkers Definitions Working Group. *Clin Pharmacol Ther.* 2001;69:89-95]. A number of candidate biomarkers of Parkinson's disease (PD) traits for diagnosis have been proposed and are being validated. These include clinical markers—objective batteries to assess for subtle motor disability. They also include neuroimaging markers—functional imaging measures that assess the degree of preservation of the presynaptic dopaminergic system with either single-photon emission computed tomography (SPECT) or positron emission tomography (PET) modalities as well as advanced magnetic resonance imaging (MRI) scans. In addition, they include biochemical markers, which measure oxidative stress and cerebrospinal fluid (CSF) α-synuclein levels, among others, and genetic or proteomic candidate biomarkers.

Biomarkers have the potential to advance our understanding of the pathophysiology of PD and accelerate drug development. However, there is a lot of confusion in this area. Below, Drs. Tanya Simuni and John Morgan offer their views on the subject.

CON Opinion

John C. Morgan, MD, PhD

Assistant Professor
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The search for biomarkers is hot in PD, whether it is imaging for dopaminergic deficits with radionuclide scans, identifying olfactory identification-deficit patterns with smell testing, or homing in on different patterns of protein expression or metabolites in biological samples that might create a molecular signature of PD.[1] Validated biomarkers will hopefully aid in both differential diagnosis and in tracking disease progression. A recently discovered biomarker, CSF fractalkine/Aβ_{1-42}, which appears to track disease severity and progression in PD, was described by Shi et al and is summarized in this issue on page 8.[2] Hopefully, this or other biomarkers can be used as surrogate endpoints in clinical trials to determine the effect of a therapeutic intervention in PD—thereby identifying disease-modifying therapies.

While biomarkers/surrogate endpoints may predict response to a pharmacologic intervention in PD, there are some recent examples that make this notion seemingly difficult to achieve. One of the best examples is radionuclide imaging in PD clinical trials (CALM-PD, REAL-PET, and ELLDOPA).[3] In all three of these trials, the findings of greater improvement in clinical measures with levodopa despite greater deficits in dopaminergic imaging were difficult to explain; in fact, this research may have created more questions than it has answered. Another potential example of a biomarker of PD progression is urate in blood and CSF.[4] Higher urate levels are correlated with slower disease progression in PD, but subjects in the DATATOP trial who were treated with vitamin E lacked this association despite higher levels of urate.[4] This illustrates how a single biomarker (higher urate) may not predict slower disease progression when the clinical context is changed, even slightly (addition of vitamin E therapy). Imagine how complex it can become given that patients have different co-morbidities and are taking different medications on differing genetic and environmental backgrounds.

In summary, a potential biomarker needs to be studied in large, diverse populations in various clinical situations, in patients on various drugs, and with various diseases before it is truly validated. While a potential biomarker may help serve as a surrogate endpoint, there are so many potential influences on a given biomarker, and these have to all be considered and controlled for in clinical trials and practice. Is the diagnosis correct? Is the patient on medications or supplements that interfere with measurement of the biomarker? Does the biomarker hold water in different races? Can co-morbidities alter the expression of a biomarker? Is the biomarker easily measured by various labs and in samples with various levels of degradation or volumes? Do polymorphisms in enzymatic metabolism (e.g., the cytochrome P450 system) indirectly alter expression of the biomarker by affecting drug metabolism?

All of these questions need to be addressed in the search for biomarkers that may serve as potential surrogate endpoints in PD clinical trials.

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