Imaging Studies in Movement Disorders

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Imaging presynaptic dopaminergic markers provides key insights into the pathophysiology of Parkinson's Disease (PD) and is becoming an important endpoint in clinical trials of potential disease-modifying therapies for PD. The further development of this area includes work to optimize targets for accurate and reliable measurement of disease progression. Ultimately, it may be possible to elaborate these markers to fine-tune our understanding of those patients who might be enrolled in a trial. For example, PD patients may be characterized as slow vs. fast progressors based on imaging measures, providing the opportunity to optimize the trial recruitment to demonstrate the greatest impact in Phase 2 evaluations of neuroprotective agents. Further, while dopamine degeneration is a crucial feature of PD, it is clear that there is widespread degeneration in the brain in PD and that many clinical manifestations of PD are likely not due to dopamine deficiency. It is reasonable to imagine that the characterization of additional targets outside the dopamine system could aid in both the molecular basis for disease characterization and ultimately optimization of therapeutics.

Parkinson's disease (PD) is characterized by bradykinesia, tremor, rigidity, and postural instability that progresses over the course of years.[1,2] The diagnosis of PD remains based on clinical evaluation of symptoms over time and response to therapies which augment dopamine neuronal function. Over the past decade scintigraphic imaging techniques have sufficiently matured to aid in the diagnosis of Parkinson's disease by targeting presynaptic dopamine cell markers lost in the disease.[3] Perhaps more important, neuroimaging can now offer important insights into the natural history of Parkinson's disease. This has complemented the development of newer treatment strategies whose aim is to interrupt cellular mechanisms implicated in the disease process.[4-7] Both single photon emission computed tomography (SPECT) and positron emission tomography (PET) have developed as means to monitor disease progression and to advance the pharmacotherapeutics of PD by aiding in the assessment of potentially neuroprotective or neurorestorative therapies. The role of imaging is becoming increasing important both from the perspective of early and accurate diagnosis of PD and the potential use as a biomarker of disease status, particularly when clinical assessments of native disease in PD patients are hampered by the inability to completely washout symptomatic medication. We will focus on recent applications and research developments in neuroimaging in PD.

DEVELOPING IMAGING TARGETS FOR MOVEMENT DISORDERS

The application of imaging technologies such as PET and SPECT to movement disorders has moved quickly, building upon a basic understanding of the pathophysiological changes in the Parkinson brain derived from early postmortem work. PD studies as early as 1919 described characteristic losses of nigral neurons, which were subsequently shown to comprise the nigral-striatal dopamine network. Therefore, radioligands which target presynaptic dopamine functions (dopa metabolism, dopamine transporters, and vesicular monoamine transporters) have been developed for research in PD with both positron emission tomography (PET) and single photon emission computerized tomography (SPECT).

The clinical or research question dictates the optimal radioligand and imaging modality. For detection of reduced dopamine neuronal function to aid in the diagnosis of PD, the relative large change in signal relative to controls (40%-50% loss) permits the qualitative use of presynaptic dopamine imaging markers.[8-10] On the other hand, the detection of the small loss of signal in the brain relative to baseline in a population of progressing PD patients demands more rigorous quantitative markers of disease (quantifiable and reproducible). Further, the most rigorous requirements of the imaging ligand are posed by studies which attempt to evaluate interruption in the normal progressive loss in PD which might, for example, slow the rate of the expected signal loss of 5-7% per year to 3-4% per year. The key issues for the application of a potential radioligand in PD include evaluation of brain penetration of the radioligand, the selec-

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Table 1. Comparison of Some Presynaptic Dopamine Radioligands in Parkinson's Studies

Radiopharmaceutical and Modality	^{123}I-β-CIT SPECT	^{11}C-VMAT2 PET	^{18}F-DOPA PET
Target	DA transporter	Vesicular transporter	DA turnover
Annual reduction in normal aging	0.8-1.4%	0.5%	No change
Bilateral reduction in hemiparkinson's disease	Yes	Yes	Yes
Correlates with UPDRS motor scores in cross-sectional studies	Yes	Yes	Yes
Annual loss of signal expressed as percent loss from baseline	6-13%	10%	7-12%

tivity of the radioligand for the target site, the lipophilicity and non-specific uptake, the binding properties of the radioligand to the site, and the metabolic fate of the radioligand. These properties determine the signal:noise characteristics of the radiopharmaceutical and the ability to reproducibly quantify the imaging signal.

Radiolabeled markers for the dopaminergic system that have been widely used to evaluate patients with PD include 18F-DOPA, 11C-VMAT2, and dopamine transporter (DAT) ligands.[6,11-15] The dopaminergic markers 18F-DOPA, 11C-VMAT2, and DAT ligands target different components of the pre-synaptic nigrostriatal neuron. Specific uptake with 18F-DOPA depends on the conversion of 18F-DOPA by the aromatic amino acid decarboxylase and uptake and trapping of 18F-dopamine into synaptic vesicles. This ligand is a marker for dopamine synthesis in the neuron. The vesicular monoamine transporter sequesters newly synthesized or recovered monoamines (dopamine, norepinephrine, serotonin, and histamine) from the cytosol into the synaptic vesicles thereby protecting the neurotransmitters from catabolism by cytosolic enzymes and packaging them for subsequent exocytotic release. The dopamine transporter (DAT) is a protein on the nerve terminal responsible for reuptake of dopamine from the synapse. All these markers demonstrate reduced uptake in the striatum, the location of the presynaptic nigral dopamine terminal projections. This region has a very high density of target sites thus permitting high quality quantitative signal assessment.

Even so, for dopamine ligands to be useful for assessing PD there must be a relationship between the changes in the imaging signal and the actual loss of dopamine neurons occurring as PD progresses. A number of studies have shown that the vesicular transporter and dopamine transporter are reduced in striatum in postmortem brain of PD patients.[16-18] In clinical imaging studies reductions in 18F-DOPA, 11C-VMAT2, and DAT ligand uptake in PD patients and aging healthy subjects have been shown, consistent with the expected pathology of PD and of normal aging.[19-22] More specifically, these cross-sectional clinical imaging studies in PD patients have shown loss that is asymmetric, where the putamenal reductions are more profound than those in caudate and the loss of the imaging signal in the striatum is correlated with the severity of the disease as measured by standardized motor ratings.[7,23,24] Further, 11C-VMAT2 and DAT ligands demonstrate reductions in activity with normal aging (Table 1).[1,25]

In considering the potential clinical and research role of dopamine imaging ligands in movement disorders it is useful to understand the necessary properties of the radiotracer. For example, there have been several DAT ligands based on tropane derivative of cocaine developed to assess PD and related disorders.[26-28] These ligands are chemically modified to slow down the rapid metabolism of cocaine at the ester linkage to provide more in vivo stability of the parent compound. Even so, differences in the kinetic properties of DAT radiotracers regarding plasma protein binding, penetration across the blood-brain barrier, binding affinity, selectivity for the dopamine transporter, and elimination are important to the particular applications of the ligand for imaging. For diagnostic purposes, to distinguish PD and related disorders from non-parkinsonian disorders, a visual, qualitative assessment of the spatial distribution of activity in the striatum (terminal sites) may be adequate, and properties of the tracer which facilitate the optimal acquisition of these images is required. However, the more stringent requirement of using the radiotracer as a reproducible and quantitative marker of the severity of the disease studied longitudinally or the effect of a putative disease-modifying (neuroprotective or neurorestorative) therapy is more difficult. PD progression is very slow and variable both between individuals, but also within an individual's course of disease. In this setting it is not

feasible to depend on qualitative changes in the imaging signal to accurately characterize subtle changes occurring at degenerating presynaptic dopamine neurons. To assess disease progression the quantitative properties of the radiotracer must be well-understood. Specifically, does the imaging signal provide a measure that is related to B_{max}, the density of binding sites, and/or the integrity of dopamine neurons? For some tracers absolute quantification of the dopamine neuron signal may require invasive methods involving full kinetic modeling, while other tracers have a pharmacokinetic profile, that simplifies the methods for signal quantification. Again, citing the example of DAT tracers, faster washout from specific binding sites causes simple brain tissue ratio techniques to overestimate the density of binding sites in healthy striatum relative to PD, although as result this property may permit better visual discrimination of diseased from control cases.[29] A radioligand optimized for visual discrimination of PD from non-PD may not be well-suited to quantitative characterization of progressing disease.

An extensive body of clinical research has been performed with 18F-DOPA, a PET marker of dopamine metabolism demonstrating the feasibility of detecting changes early in disease, serially in PD patients studied longitudinally, and measuring the effects of possible disease-modifying therapies on dopamine system degeneration. Of the DAT tracers in development, 123I-β CIT, 123I FP-CIT, 123I altropane, and 99mTc-TRODAT have been the most widely evaluated dopamine transporter agents for SPECT imaging and 18F-CFT (WIN 35, 428) for PET.[8,9,15,30,31] None of these tracers is commercially available as yet in North America, although one tropane derivative of cocaine (FP-CIT, DATSCAN®) is available as a 123I labeled tracer in Europe. The vesicular transporter 11C-VMAT2 is another presynaptic marker with a limited but increasing number of PD studies suggesting the feasibility of measuring disease progression.[21] This marker has been proposed to provide the potential additional benefit of a marker that is not regulated by the usual medications PD patients must take for symptomatic improvement even at relatively early stages of the disease.[32] However, the true relevance of this theoretical benefit remains to be demonstrated.

Finally, the use of PET or SPECT is ultimately determined by the specific study questions and study design. While, PET cameras have better resolution than SPECT cameras, SPECT studies may be technologically and clinically more feasible, particularly for large Phase III clinical studies and in clinical practice. PET studies may benefit from greater flexibility in the range of radiopharmaceuticals that can be tested, but SPECT has the advantage of longer half-life radiopharmaceuticals necessary for some studies and potentially lower cost.

DIAGNOSIS OF PARKINSON'S

The diagnosis of Parkinson's disease remains a clinical assessment made difficult by the variability of the disease presentation, rate of progression, and response to medications. Based on long-term clinic pathologic studies the diagnoses most commonly mistaken for PD are Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA). More important, in the early in the phase of PD the diagnoses most commonly mistaken for PD are essential tremor, vascular parkinsonism, drug-induced parkinsonism and Alzheimer's disease.[33] It has been reported that as many as 35% of those initially felt to have PD by generalists are incorrectly diagnosed. Prevalence estimates for clinically evident parkinsonism in similarly aged subjects are much lower at around 3%.[34]

Neuroimaging holds the promise of improving diagnosis by providing an assessment of the dopaminergic system in early disease. In addition, imaging potentially also addresses questions about the basic pathophysiology of the disease process which is otherwise difficult to obtain. Studies with 18F-DOPA PET, and 123I-β CIT SPECT indicate a reduction in radiotracer uptake of approximately 50-70% in the putamen in PD subjects.[21,30,31,35-39] However, at the threshold of diagnosis patients with symptoms of PD show reduction in putamenal 18F-DOPA or dopamine transporter activity of 40-60% rather than 80-90%[40] originally assumed based on pathology studies. This provides further support for developing therapies to protect the remaining 50% of dopaminergic neurons not yet affected at the time of diagnosis.

How well do these agents distinguish those with PD from those without illness? In a number of studies the dopamine and vesicular transporter ligands and 18F-DOPA distinguished between PD and healthy subjects with a sensitivity of $>$ 95%.[4,31,38,41-44] Furthermore, the reduction in both dopamine and vesicular transporter and 18F-

DOPA imaging activity correlated with well-defined clinical rating scales of PD severity. Within the PD group across the spectrum of disease severity the best correlation of the imaging measures is with bradykinesia.[7] Pathological evaluations suggest bradykinesia is a sensitive measure of the extent of neuronal loss.

The more clinically important question is how well does imaging serve to render an accurate diagnosis in a typical clinical setting, in early disease, when the greatest percentage of misdiagnoses occurs? A number of studies have addressed this question. Imaging appears to be useful in distinguishing PD from essential tremor, a common disorder which does not progress over time.[42,45] In addition, imaging may also be useful in special diagnostic situations such as psychogenic, drug-induced, traumatic or vascular parkinsonism, in distinguishing these syndromes without a presynaptic dopamine deficit from PD.

A more challenging diagnostic problem is the distinction between the more specific diagnosis of PD and other related neurodegenerative disorders categorized as Parkinsonism or Parkinson's syndrome. The most common etiologies of Parkinson's syndrome are progressive supranuclear palsy, multi-system atrophy, cortical basal ganglionic degeneration, and diffuse Lewy body disease. In total these represent about 15-20% of patients with apparent PD.[1,30,36,46] The extent of imaging signal loss alone does not tease apart Parkinson's disease from other causes of Parkinson's syndrome. Nonetheless, the pattern of loss in Parkinson's syndrome is less region-specific than in idiopathic PD, the putamen and caudate more equally effected.[47] Left and right striatal radiotracer uptake in these disorders is also more symmetric than in idiopathic Parkinson's disease. For example, dopamine transporter imaging can discriminate between Parkinson's disease and other causes of Parkinson's syndrome with a sensitivity of about 75-80%.[38,48] Post-synaptic D2/D3 receptors densities are normal or slightly elevated in idiopathic PD, while the more extensive changes in the dopamine system in the parkinsonism are reflected in reductions in post-synaptic dopamine receptor binding. Studies have suggested a strategy of imaging presynaptic and postsynaptic dopaminergic sites or metabolic imaging as a possible means to distinguish Parkinson's disease from other related Parkinsonian syndromes.

PARKINSON'S DISEASE PROGRESSION

Of major interest in the clinical application of dopaminergic imaging markers in PD has been the prospect of improving understanding of the longitudinal course of the disease. This is highly relevant from the perspective of interventions that attempt to slow the rate disabling symptoms emerge and progress. In fact, much of drug development in neurodegenerative disorders like PD has been away from monoamine-replacement strategies for symptom amelioration, toward discovery of treatments which directly hinder the process of on-going dopamine neuronal loss.

There are a number of recent studies using imaging of the nigrostriatal dopaminergic system to monitor disease progression in PD. Longitudinal studies of PD progression involving serial imaging in both 18F-DOPA and dopamine transporter imaging (123I-β CIT and 11C-CFT) using both PET and SPECT have shown an annualized rate of reduction in striatal 18F-DOPA, 18F-CFT or 123I-β CIT uptake of about 6% to 13% in PD patients compared with 0% to 2.5% change in age-matched healthy controls (Fig 1).[5,6,15,49-51]

Another way of looking at the question of disease progression is from analysis of the changes detected on imaging studies of hemi-PD subjects imaging. Most patients with PD present with unilateral symptoms that become bilateral over the course of the disease, although significant asymmetry of severity persists throughout the illness course. Imaging studies in early hemi-PD show a reduction in 18F-DOPA and dopamine transporter uptake of approximately 50% in the effected putamen and of 25-30% in the unaffected putamen.[40] Therefore, the imaging measures are picking up changes in dopaminergic function on both sides of the brain, even prior to symptom manifestation on the clinically unaffected side. The time required for most patients to progress clinically from unilateral to bilateral symptoms is 3-6 years. It likely that the loss of these in vivo imaging markers of dopaminergic degeneration in the previously unaffected putamen will progress at about 5-10% per annum.

Imaging markers of PD can serve a potentially unique role in providing a window on the state of illness from the perspective of drug development.[52] Clinical trials designed to establish a disease-modifying effect of a treatment in PD are extremely difficult to design and execute. The major reasons for this are: 1) the rate of clinical progres-

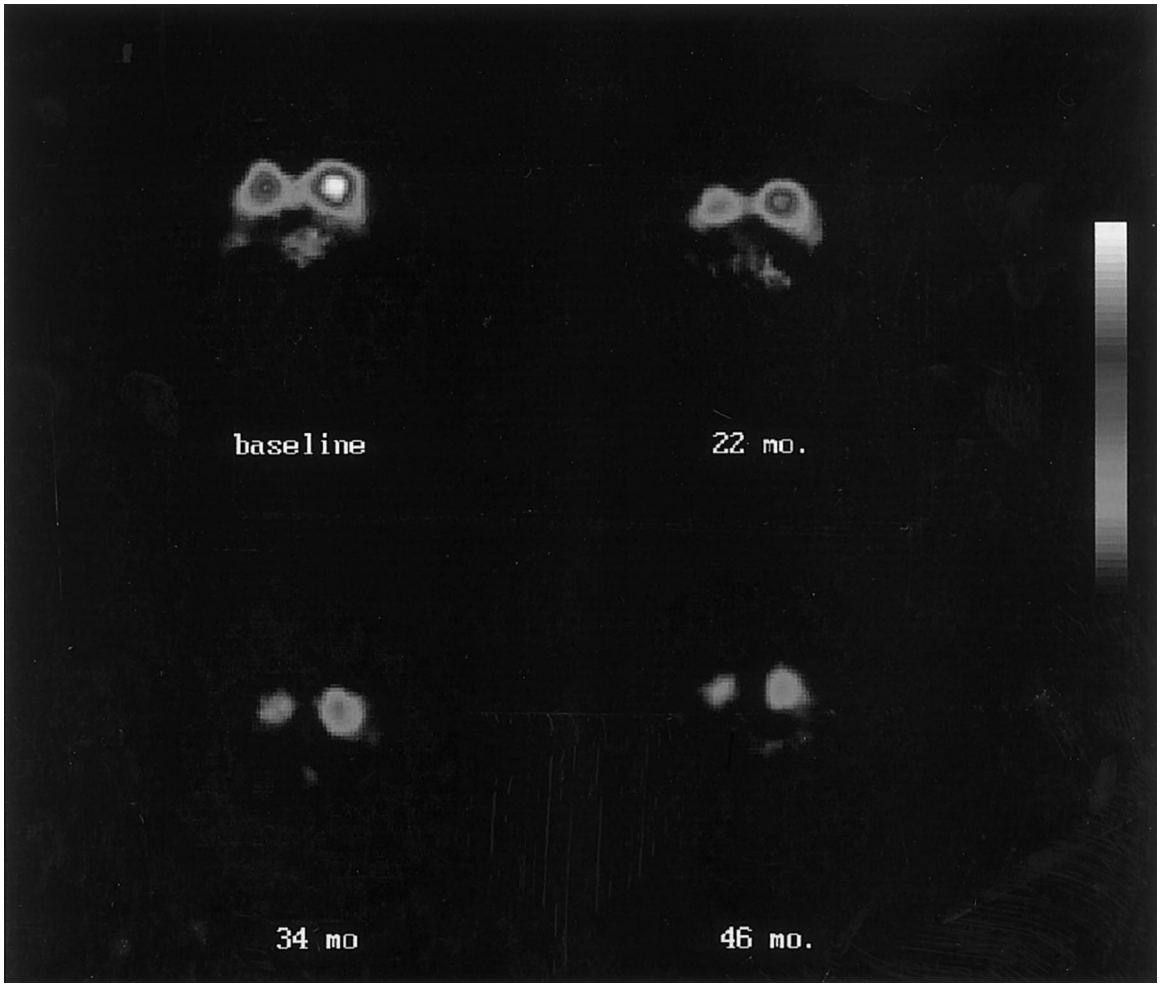

Fig 1. Parkinson disease patient imaged serially over approximately four years with 123-I β-CIT SPECT demonstrates serial reduction in radiotracer uptake in the striatum. Note relatively greater involvement in the putamen (posterior striatum) and left/right asymmetry of uptake which persists over four years.

sion of PD is slow, highly variable, and unpredictable; 2) clinical assessments are confounded by the problem of completely washing-out patients from their symptomatic drugs to evaluate the true severity of disease; and 3) trials must be of sufficient duration (1-2 years) to have adequate time to measure the progressing disease and potential beneficial effect of the putative neuroprotective agent. In trials of this sort clinical endpoints for progressive functional decline in PD have included UPDRS in the 'defined off' state or after drug washout up to two weeks, time to need for dopaminergic therapy, or time to development of motor fluctuations.[53]

In considering the use of imaging endpoints in disease-modifying trials in PD the sample size required depends on the expected effect size of the drug and the duration of exposure to the treatment. The effect of the drug may be expressed as the percentage reduction in rate of loss of the imaging marker in the group treated with the study drug compared with the control group. The sample size needed to detect a 25%-50% reduction in the rate of loss of 18F-dopa or 123I-β CIT uptake during a 24 month interval ranges from approximately 30-120 research subjects in each study arm for a placebo-controlled trial.[54]

There are several important caveats in the study design and interpretation of neuroimaging studies for assessing neuroprotective therapies in PD. First, imaging outcomes in studies of PD patients are biomarkers for dopamine system function, but

are not true surrogates for drug effects in PD patients. Ultimately, in the absence of a measurable benefit to the patient based on clinical measures, the applicability of the imaging measure becomes irrelevant. It is possible for discordance to arise between the neuroimaging outcomes and the clinical measures. This is well-described in hemi-PD patients where the imaging measures show bilateral striatal changes, hence the striatum ipsilateral to the affected side is discordant with the unaffected side. The progression of clinical symptoms will eliminate this discordance, as this largely reflects the high sensitivity of the imaging measures for picking up alterations in dopaminergic systems which may be still well-compensated by the brain.

A second caveat is that imaging outcomes of disease progression may be confounded by pharmacologic effects of the study drug. For example, some pre-clinical and clinical studies evaluating the effect of dopamine agonists and antagonists and levodopa suggest possible regulation of both the dopamine transporter and dopamine turnover, while other studies show no effects.[10,55-61] The applicability of many preclinical studies to human imaging studies is debatable due to variable and short-duration of exposure to drugs, small numbers of test animals, supra-pharmacological dosing, species differences, and methodological differences in the measures of dopamine transporter. Imaging studies in PD patients that directly assessed the potential short-term regulation of imaging ligands by common PD medications do not show regulation of dopamine transporter ligands or 18-F-Dopa uptake by levodopa or dopamine agonists.[61] In the CALM-PD study of PD patients there was no significant change in 123I-β CIT uptake after 10 weeks of treatment with either pramipexole (dosage 1.5-4.5 mg) or levodopa (dosage 300-600mg), consistent with previous studies evaluating levodopa and selegiline effects after 6-12 weeks.[62] Another study demonstrated that treatment with pergolide for 6 weeks similarly showed no significant changes in 123I-β CIT striatal, putamen or caudate uptake, but an insignificant trend toward increased 123I-β CIT uptake.[63] In a small PET study with the dopamine transporter ligand 11C RTI-32, there were significant reductions from baseline in striatal DAT after 6 weeks of treatment with both levodopa and pramipexole, but also with placebo.[64] In summary, while these clinical studies do not demonstrate significant regulation of the dopamine transporter uptake, they do not entirely exclude a significant short-term treatment-induced change in dopamine transporter nor do they address the chance that pharmacologic effects may occur in longer-term studies.

A third caveat for consideration in conducting disease-modifying treatment trials in PD with imaging measures is the rigor with which the reliability of the imaging measures are characterized. It is important to understand the test-retest reproducibility of the imaging measures to know the effect of this variance on the ease with which the changes in the pathophysiology may be measured. Test-retest studies using current technology and analyses methodology show good test-retest reproducibility of approximately 3-5% for 18F-DOPA or 11C-VMAT2 studies and 5-7% for 123I-β CIT SPECT.[65-69]

These caveats notwithstanding, imaging biomarkers have become an increasing useful method to assess the potential disease modifying effect of experimental drugs for PD. A number of drugs are in early clinical development, including coenzyme Q10, neuroimmunophilin A, riluzole, CEP 1347, and pramipexole and ropinirole. The putative mechanisms of action of each of these agents are different.

As an example of the use of neuroimaging in the assessment of agents with disease modifying potential two similar studies were recently completed evaluating the effect of initial treatment with a dopamine agonist pramipexole (CALM-PD CIT) or ropinirole (REAL-PET)) or levodopa on the progression of PD as measured clinically and by 123I-β CIT or 18F Dopa imaging.[62] These two clinical imaging studies targeting dopamine function with different imaging ligands and imaging methods both show slowing in the rate of loss of 123I-β CIT or 18F Dopa uptake, in early PD patients treated with dopamine agonists compared to levodopa. The relative reduction in the percent loss from baseline of 123I-β CIT uptake in the pramipexole versus the levodopa group was 47% at 22 months, 44% at 34 months, and 37% at 46 months after initiating treatment. The relative reduction of 18F Dopa uptake in the ropinirole group versus the levodopa group was 35% at 24 months. There were no placebo controls in either study, so the data cannot distinguish between the possibili-

ties that dopamine agonists reduce the rate of signal decline of that 1-dopa enhances the rate of signal loss. Nonetheless, the feasibility of conducting these large-scale imaging trials over relatively long periods and using imaging biomarkers as an important outcome measure is well-demonstrated.

Three important questions from these first trials include; 1) why are there are differences in the clinical measures of disease severity and the neuroimaging measures?; 2) should there be a role for imaging as a potential inclusion criteria for initial enrollment into these trials?; and 3) how should clinical trial design be optimized to avoid the potential confound of disease-modifying effects of symptomatic agents? Concerning the first of these, both these trials show no correlation between the percent change from baseline in the imaging outcome and the change from baseline in UPDRS at 22-24 months. There are several explanations for the lack of correlation; 1) the UPDRS is confounded by the effects of the patient's anti-parkinson medications and the washout does not eliminate the long duration symptomatic effects of these treatments; 2) in early PD the temporal patterns for rate of loss of dopamine transporter or 18F Dopa and the change in UPDRS may not be in-phase as noted in the hemi-PD studies above. The CALM-PD study showed only at later time points (46 months) the loss of striatal 123I-β CIT uptake from baseline was significantly correlated ($r = -0.40$, $p = 0.001$) with the change in UPDRS motor rating suggesting that the correlation between clinical and imaging outcomes begins to emerge with longer monitoring.

A second lesson from these studies is the observation that the gold-standard of clinical diagnosis at study enrollment will not screen out subjects without PD. The earlier the stage of illness course evaluated, the larger the potential for misdiagnosis. Imaging measures of dopaminergic function may show striatal uptake out of the range seen in PD. Should the imaging measures be used as another means for phenotyping individuals with respect to study enrollment? It seems feasible that this might be a consideration in future studies of disease-modifying treatments which may proceed for several years as a means to reduce potential long-term exposures to investigational agents in subjects who may not have the disease in question.

The third lesson from these trials is how to manage potential confounding effects of symptomatic medication like the dopamine agonists, in trials evaluating neuroprotective agents. If either 1-dopa is neurotoxic or pramipexole or ropinirole slows down disease progression, then it is important to consider the impact of these agents in future trials of disease-modifying agents, since both treatments are common in PD. In this regard, designing trials which standardize symptomatic therapies to the extent clinically feasible in patient participating may be important.

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