Parkinson's Disease:
Functional Imaging of the Dopamine Pathway

The diagnosis of movement disorders and neurodegenerative diseases can be problematic for clinicians and radiologists alike. There is considerable overlap in the early presentation of these diseases, especially when tremor is absent or atypical in character. Routine anatomic imaging is insensitive and early imaging findings are typically absent or non-specific. Functional nuclear medicine imaging of the dopamine pathway using I-123 Ioflupane (DaTSCAN) SPECT and F-18 Dopamine (DOPA) PET offers renewed hope in categorising these diseases as Parkinsonian (degenerative) or non-Parkinsonian (non-degenerative) in etiology.

Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer disease (AD) affecting approximately 1 million Americans and 4 million people worldwide. It affects 0.5-1.0% of the population between 65 and 69 years old, and 1-3% of the population older than 80. The cause of idiopathic PD is the degeneration of neurons which connect the subtantia nigra to the corpus striatum, the so called nigrostriatal pathway. These neurons control the release of the neurotransmitter dopamine to receptor cells which affect motor function. Pre-synaptic dopamine transporter proteins are located on the cell membranes of these terminal neurons, which continuously reuptake dopamine from synaptic clefts after the completion of interaction with dopamine receptors on the post-synaptic neuron. Non-degenerative Parkinsonian syndromes may be drug-induced or vascular as a result of ischemic insults to the pathway.

DaTSCAN SPECT and F-18 DOPA PET image different points along the dopamine pathway. The I-123 isotope of iodine bound to fluoropropyl-carboxymethyl-iodophenyl nortropane or FP-CIT, sold under the trade name DaTSCAN, binds reversibly to human recombinant dopamine transporters and is blocked by dopamine reuptake inhibitors. The dopamine transporter is thus a surrogate marker for dopaminergic nigrostriatal neurons. Fluoro-DOPA is an analog of levo-DOPA (L-DOPA). Dopamine in circulation does not cross the blood-brain barrier of the central nervous system. L-DOPA is carried across by the neutral amino acid transport system. L-DOPA is then converted to dopamine in the brain by L-aromatic amino acid decarboxylase. Dopamine is stored in pre-synaptic intraneuronal vesicles and released when the nerve cell fires. Flourine-18 bound to dopamine is the PET imaging analog.

Both DaTSCAN SPECT and F-DOPA PET assess the pre-synaptic dopaminergic system. DaTSCAN images correlate with dopamine transporter density in the corpus striatum. F-DOPA images correlate with the activity of the decarboxylating enzyme and the storage capacity of dopamine in these same structures. Early in PD, dopamine transport is downregulated to preserve pre-synaptic dopamine, making DaTSCAN SPECT more sensitive in detection. Conversely, the decarboxylating enzyme can be upregulated as a compensatory mechanism and F-DOPA PET imaging may be falsely negative early in PD. Both tests are highly effective in differentiating PD and the atypical Parkinsonian syndromes (APD) multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration and dementia with Lewy bodies from non-degenerative essential tremor (ET) and drug-induced Parkinsonism.

While F-DOPA PET has certain imaging advantages over DaTSCAN SPECT, its use is limited mostly to academic centres with on-site or near-site cyclotrons. The isotope fluorine-18 has a half-life of less than two hours and its binding to L-DOPA is a rigorous process. Incubation time between injection and imaging is less than one hour and the spatial resolution of PET is superior to that of SPECT. The isotope iodine-123 has a half-life of 13 hours and is readily available via commercial distribution. The thyroid gland is blocked with Lugol's solution or potassium iodide prior to radioactive iodine administration. Imaging requires incubation of the I-123 DaTSCAN agent between three and four hours. The gamma photon energy of 159 keV is standard and SPECT images are reconstructed for viewing in the transverse plane.

It is generally accepted that the motor symptoms of PD occur after 60-80% of dopamine-producing neurons are lost and that loss proceeds at a rate of 6-13% per annum. Degeneration occurs in dopaminergic cells which originate in the substantia nigra and terminate in the corpus striatum. The disease process produces loss of striatal dopamine and the dopamine transporters that collect spent dopamine from the synaptic cleft. The loss of neurons in the striatal terminals proceeds from lateral to medial, thereby affecting the posterior putamen before the caudate head. PD and APS typically produce asymmetric motor symptoms. The imaging abnormalities are correspondingly variable and can be unilateral, bilateral or bilaterally asymmetric. In essential tremor and drug-induced Parkinsonism there is no nigrostriatal dopaminergic cell loss, therefore imaging by either modality is normal.

DaTSCAN SPECT provides an *in vivo* marker of dopaminergic neuronal degeneration which helps differentiate PD and APS from ET, drug-induced Parkinsonism and other non-Parkinsonian syndromes. There is no clinical biomarker for the pathologic substrate of PD, the intraneuronal inclusion of Lewy bodies in the substantia nigra compacta. Clinical history, physical examination and a positive response to L-dopamine remain the standards for diagnosis. PD is generally characterised by an asymmetric rest tremor, slow movements (bradykinesia), stiffness (cogwheel rigidity)

and problems with walking or balance (postural instability). A positive clinical diagnosis is established by bradykinesia and one additional cardinal feature plus a positive response to dopamine therapy. In ET, tremor is the primary symptom, typically symmetrical and produced with action or upon standing.

Sometimes PD patients have no tremor or a postural tremor that mimics ET. Occasionally ET patients have an asymmetric tremor, rest tremor or cogwheeling rigidity that mimics PD. The overtreatment of non-PD patients with anti-Parkinsonian medications is estimated at 15-47 %. Post-mortem confirmation of a non-PD diagnosis in a hospital study of patients treated for PD has been reported as 10-24 %. The DaTSCAN can be a valuable tool in reducing the overdiagnosis of PD. A negative DaTSCAN in the presence of tremor has a negative predictive value of 87.5 %. Conversely, an abnormal DaTSCAN has a positive predictive value for PD or APS of virtually 100 %.

As the imaging of movement disorders plays a larger role in the aging demographic of our clinical practices and as disease documentation prior to deep brain stimulation becomes a medical requirement, it is helpful to become familiar with the newer functional molecular imaging tools at our disposal. In addition, since both Parkinson disease and atypical Parkinsonian syndromes can produce cognitive decline, the functional modalities FDG-PET and DaTSCAN SPECT will become increasingly beneficial to avoid unnecessary and occasionally harmful therapies.

References

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