123I-Ioflupane/SPECT binding to striatal dopamine transporter (DAT) uptake in patients with Parkinson’s disease, multiple system atrophy, and progressive supranuclear palsy

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Abstract
We used SPECT and the tracer 123I-Ioflupane to measure dopamine transporter (DAT) binding in the caudate nucleus and the putamen of 70 patients with Parkinson’s disease (PD), 10 with multiple system atrophy (MSA-P type), and 10 with progressive supranuclear palsy (PSP). Data were compared with 12 age-matched control subjects. We found significant reductions in mean striatal values in all three forms of parkinsonism. However, decrements were significantly greater in PSP (0.51±0.39, p<0.01) compared with MSA-P (0.70±0.33) and PD (0.95±0.38). No differences were found between MSA and PD. Putamen/caudate ratios were greater in PSP (0.83±0.12, p<0.01) than in PD (0.51±0.11), suggesting a more-uniform involvement of dopamine nerve terminals in both caudate nucleus and putamen. Our results confirm that DAT binding can provide an accurate and highly sensitive measure of dopamine degeneration. PSP patients may show a different pattern of neuronal loss compared with MSA and PD.

Degenerative parkinsonian syndromes are characterized by progressive loss of dopaminergic neurons in the substantia nigra. Neuroimaging studies allow in vivo assessment of the nigrostriatal dopaminergic system and the extent of neuronal loss in these disorders. Tracers that bind selectively to dopamine cells have been applied together with positron emission tomography (PET), and more recently single-photon emission computed tomography (SPECT), for clinical and research purposes. Historically, ¹⁸F-fluorodopa/PET was considered the gold standard for assessment of dopaminergic denervation [1, 2]. There are, however, technical limitations to the use of this tracer. Firstly, PET is available at few centers. Secondly, it is likely that dopa-decarboxylase activity is upregulated early in the disease process, resulting in an underestimation of dopaminergic neuronal loss. Therefore tracers that utilize the SPECT technique and bind selectively to the dopamine transporter (DAT) may be better suited and provide more-accurate estimation of degeneration. Several tracers that bind to DAT and utilize SPECT are available; they are all cocaine derivatives. The most widely used are [¹²³I]β-CIT and 123I-Ioflupane ([¹²³I]FP-CIT) [3, 4]. The main advantage of 123I-Ioflupane is that a steady state allowing SPECT imaging is reached 3 h after a single bolus injection of the radioligand, compared with the 18–24 h required for [¹²³I]β-CIT. Therefore DAT imaging with 123I-Ioflupane can be completed the same day.

Several studies have demonstrated the usefulness of 123I-Ioflupane SPECT imaging in the diagnosis of parkinsonism. A sensitivity of 97% has been reported for the identification of nigrostriatal degeneration in Parkinson’s disease (PD) [5]. Limited data are available on DAT binding in other degenerative parkinsonisms, such as progressive supranuclear palsy (PSP) or multiple system atrophy (MSA) [6].

Patients and methods
We studied DAT binding with 123I-Ioflupane SPECT in 70 PD patients (age 62±13 years, disease duration 5±4 years), 10 MSA-P patients (age 60±8 years, disease duration 4±2 years), and 10 PSP patients (age 64±8 years, disease duration 4±3 years). UPDRS scores were obtained in all patients in “off” condition.

Brain SPECT was performed with a dedicated triple detector gamma camera (Prism 3000, Philips) equipped with ultra-high-resolution fan beam collimators. 123I-Ioflupane (DATScan) (110–140 MBq) was administered intravenously 30–40 min after thyroid blockade. SPECT studies were acquired 3–4 h later and reconstruction was performed by applying an iterative algorithm, followed by tridimensional filtering. Transaxial sections were attenuation corrected and reoriented with respect to the canthomeatal plane. Four adjacent sections, including striatum and occipital cortex, were summed in a single 2.56-cm thick slice for quantitative analysis. Irregular regions of interest (ROIs) were drawn on both striata, putamina, heads of caudate nuclei, and mesial occipital cortices. Ioflupane specific binding ratio was expressed as (striatal ROI counts – occipital ROI counts)/occipital ROI counts and calculated for the whole striatum, putamen, and caudate head of each hemisphere. We also calculated putamen/caudate ratios for each subject.

Results
We found significant decrements in DAT binding in the striatum of PD, MSA-P, and PSP patients compared with healthy controls. Mean striatal values were 0.95±0.38 in PD, 0.70±0.33 in MSA, and 0.51±0.39 in PSP. Healthy controls have striatal uptake values >1.7. An example of 123I-Ioflupane SPECT in a control subject, a PD patient, and a PSP patient is...
shown in Fig. 1. We found that striatal values were significantly lower in PSP than PD ($p<0.01$). No differences were found between MSA-P and PD. Putamen/caudate ratios were greater in PSP ($0.83\pm0.12$, $p<0.01$) than in PD ($0.51\pm0.11$) and MSA-P ($0.60\pm0.12$). In PD patients we found a significant correlation with UPDRS motor scores ($p<0.001$). No correlation was found in the MSA and PSP cohorts.

**Discussion**

We found significant decrements of striatal DAT in PD, MSA-P, and PSP patients. We can confirm that $^{123}$I-Ioflupane SPECT binding is a sensitive measurement of the dopaminergic system in degenerative parkinsonism. Moreover, we found a different pattern of degeneration between PD and PSP. A similar finding has been previously reported with the tracer $^{18}$F-fluorodopa in PSP patients [2]. The greater decrements in the putamen than in the caudate nucleus in PD patients is consistent with neuropathological data showing that the bulk of nigral loss affects the dopaminergic neurons projecting to the putamen. PSP is characterized by a more profound and diffuse dopaminergic loss.

We were able to show a significant correlation between striatal uptake and UPDRS motor symptoms in PD, suggesting that $^{123}$I-Ioflupane SPECT is also a specific marker of disease progression. The absence of a significant correlation in other forms of parkinsonism was probably related to the fact that the majority of our MSA and PSP patients had already marked disease at the time of SPECT scanning.

The differential diagnosis of different forms of parkinsonism is not easy, particularly at an early stage. Although a recent report suggests that in a specialized tertiary center diagnostic accuracy can be as high as 90%, clinical pathological studies in the 1990s found the accuracy of clinical diagnosis to be only 76% [7], and the rate of misdiagnosis at early stages of the disease may exceed this figure. In a recent community based study conducted in a general practice, the diagnosis of clinically probable PD could only be confirmed in 53% of patients taking antiparkinsonian drugs [8]. Such misdiagnosis can lead to inappropriate management strategies that may include further unnecessary investigations.

In conclusion, studies of the pre-synaptic dopaminergic system may prove clinically useful in assessing the presence and extent of nigro-striatal loss in different forms of degenerative parkinsonism. Additional neuroimaging investigations, such as $^{123}$I-IBZM for striatal dopamine receptors or 1,ST magnetic resonance imaging, may help to characterize these patients. The finding of a uniform and profound DAT loss in the whole striatum seems to be specific to PSP.

**References**