Radiotracer imaging of dopamine transporters and presynaptic dopamine synthesis in parkinsonian syndromes

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Introduction

The prevalence of idiopathic Parkinson’s disease (IPD) is 84-164 per 100,000 for Caucasians, whereas the annual incidence is 8.7-20 per 100,000.1 Both figures increase with age. These figures show that IPD is and will be one of the major neurological causes of morbidity, especially with an increasing mean age of the population. The development of possible pharmacological treatments to retard the progression of IPD, such as selegiline and dopamine (DA) agonists rather than L-DOPA, has increased the need for a reliable outcome measure to assess progressive loss of the dopaminergic (DAergic) system, to monitor the efficacy of treatment and to diagnose the disease during the preclinical phase so that treatments can be implemented before irreversible loss of DAergic neurons occurs.2 The preclinical phase in IPD may be as long as 20-40 years. Neuroimaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) provide such objective outcome measures.3-5 The presynaptic site can be labeled with probes for the DA transporter (DAT) or the synthetic enzyme aromatic l-amino acid decarboxylase (“DOPA decarboxylase”).

[123I]ßCIT SPECT as marker for IPD

With [123I]2ß-carbomethoxy-3ß-(4–iodophenyl)tropane ([123I]ßCIT or [123I]RTI-55) SPECT, acceptable clinical-epidemiologic characteristics of a preclinical marker of later onset of IPD, showing clinical-pathological relevance to the process, have been met.3,4,6,7 [123I]ßCIT SPECT imaging of DAT may be useful for: (1) diagnosing early or pre-symptomatic stages of IPD, (2) monitoring progression severity in IPD over time, (3) assessing the efficacy of putative neuroprotective agents, (4) revealing the extent of striatal involvement in IPD and other parkinsonian syndromes, and (5) following growth or rejection of fetal tissue transplanted into IPD patients (see below).

Correlation with neuronal cell counts or dopamine levels

As mentioned above, decreased DAT densities have been observed in putamen and caudate nucleus in IPD patients, closely paralelling losses of DA.8,9 Both the decrease of tissue DA levels and [³H]2ß-carbomethoxy-3ß-(4–fluorophenyl) tropane ([³H]ßCFT or [³H]WIN-35,428) binding to the DAT showed similar medial to lateral gradients in the striatum and more severe losses in the putamen compared to the caudate (Kaufman and Madras 1991; Kish et al. 1988). [¹²³I]ßCIT SPECT studies performed in IPD patients have confirmed the relative selective loss of DAT in the putamen.10-14

Sensitivity and specificity, and positive and negative predictive values for IPD

Hemiparkinson patients demonstrate reduced striatal uptake contralateral and ipsilateral to motor symptoms suggesting [¹²³I]ßCIT may be sensitive to preclinical changes in DAT.11,12,15,16 The V 3 “ (e.g. the ratio of {striatum-occipital cortex} over occipital cortex during a state of equilibrium), the putamen/caudate ratio and the contralateral/ipsilateral ratio for putamen and caudate were significantly reduced in 28 IPD patients compared with 27 healthy controls.14 Discriminant function analysis using V 3 “ for ipsilateral and contralateral caudate and putamen correctly classified 54 of the 55 cases; when age-correction of the data was performed, all cases were correctly identified. Age-corrected V 3 “ in the putamen contralateral to the side of sign onset provided a particularly good group separation with only 18% unaccounted variance. Similar analyses for the putamen/caudate ratio and the contralateral/ipsilateral ratio for putamen and caudate correctly classified 96% and 80% of the subjects, respectively.

Correlation with onset of symptomatic IPD and with severity of symptoms

[¹²³I]ßCIT SPECT in five IPD patients showed greater losses in the striatum contralateral to the side of the body with initial symptoms.15 In eight early IPD patients with exclusively hemiparkinsonism, [¹²³I]ßCIT striatal uptake was reduced by about 53% contralateral and by 38% ipsilateral to the clinically symptomatic side, when compared with eight age and sex matched healthy subjects (Marek et al. 1996). The reduction in [¹²³I]ßCIT uptake was greater in the putamen than in the
caudate. These data were confirmed independently in 15 early untreated IPD patients and 16 early untreated IPD patients, and indicate that \[^{123}\text{I}\]ßCIT SPECT may be useful in identifying individuals with developing DAergic pathology prior to the onset of motor signs.

In 28 L-DOPA-responsive IPD patients, the degree of abnormal striatal uptake of \[^{123}\text{I}\]ßCIT, expressed as both ipsilateral and contralateral \(V_{p}^{*}\) in both putamen and caudate, was significantly correlated with the total Unified Parkinson’s Disease Rating Scale (UPDRS) score and with the Hoehn-Yahr stage. Both UPDRS motor subscores and bradykinesia were strongly correlated with the \(V_{p}^{*}\) measures. The uptake in the putamen was relatively more reduced than in the caudate. Also, the asymmetry (based on the side where the parkinsonian signs started) was larger in the putamen than in the caudate. These findings have been reproduced in small groups of IPD patients discriminated as early (Hoehn and Yahr scores 1-2) and late IPD patients (Hoehn and Yahr scores 2.5-4; disease history > 10 years), in 34 previously untreated IPD patients (Hoehn and Yahr scores 1-3), and in a large group of 113 IPD patients (Hoehn and Yahr scores 1-5).

### Differential diagnosis

It has been suggested that the elevation of the caudate/putamen ratio and marked asymmetry of \[^{123}\text{I}\]ßCIT activity may be useful in distinguishing IPD from atypical parkinsonian syndromes such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) patients compared to 113 IPD patients, but not sufficiently to differentiate IPD from MSA or PSP. Also, posterior putamen/caudate ratios by \[^{11}C\]ßCIT PET allowed discrimination of six PSP patients from six IPD patients. The differential diagnosis between IPD on the one hand and MSA on the other hand can be further improved by adding imaging with presynaptic markers such as \[^{18}F\]FDOPA PET and \[^{123}\text{I}\]ßCIT SPECT to DA D_{2} receptor imaging. With both \[^{123}\text{I}\]ßCIT and \[^{123}\text{I}\]IBZM SPECT in 50 unselected patients with parkinsonian syndromes, both sensitivity and specificity were 86%.

### Other markers for IPD

Similar findings as for \[^{123}\text{I}\]ßCIT SPECT were observed with \[^{11}C\]ßCIT PET in nine IPD patients when compared with three healthy controls. However, because of the short half-life of \(^{11}\text{C}\), only the first part of a prolonged accumulation process could be visualised. Therefore, ßCIT may be better suited for SPECT studies than for PET.

With SPECT using the N-fluoropropyl, methyl ester of ßCIT, i.e. \[^{123}\text{I}\]FPCIT, the loss of striatal DAT was measured in five non-medicated IPD patients versus five healthy controls. Assayed at 3 hours after the intravenous injection of \[^{123}\text{I}\]FPCIT, the patients showed reduced signal in both caudate nucleus and putamen. The ratios of specific to nonspecific uptake were consistently 2.5-fold lower than for \[^{123}\text{I}\]ßCIT. However, when expressed as a percentage of the uptake ratio found in healthy controls the decrease in the IPD patients was similar for both tracers.

An elaboration of the \[^{123}\text{I}\]FPCIT SPECT study in six early IPD patients (Hoehn and Yahr score 1-2), 12 patients with advanced IPD (Hoehn and Yahr score 2.5-4; disease history > 10 years), and six healthy age-matched controls revealed that the specific to non-specific striatal uptake ratios correlated with the Hoehn and Yahr stage.

Progression of IPD evolved apparently more rapidly in the putamen than in the caudate nucleus based on the relatively higher uptake of the latter area in early IPD. For all 21 early-stage and drug-naïve IPD patients, striatal \[^{123}\text{I}\]FPCIT ratios were lower than those in 14 healthy controls with more reductions in the putamen than in the caudate nucleus and more reductions contralateral than ipsilateral to the side with the most severe symptoms; the subgroup with hemi-IPD showed DAT loss even on the ipsilateral side. In this early IPD group no significant correlations were found between striatal \[^{123}\text{I}\]FPCIT ratios and disease severity. One can conclude that (1) \[^{123}\text{I}\]FPCIT allows a significant discrimination between IPD patients and age-matched controls, (2) \[^{123}\text{I}\]FPCIT seems as good as \[^{123}\text{I}\]ßCIT for this purpose, and (3) the faster kinetics of \[^{123}\text{I}\]FPCIT allow a one day protocol, which is a clear advantage over \[^{123}\text{I}\]ßCIT. One caveat is that with \[^{123}\text{I}\]FPCIT only a transient or pseudo-equilibrium is reached versus a prolonged equilibrium with \[^{123}\text{I}\]ßCIT.

This caveat was addressed in another recent study which also compared \[^{123}\text{I}\]ßCIT versus \[^{123}\text{I}\]FPCIT SPECT in six IPD patients versus five healthy controls. The major conclusions were the following. (1) The nonspecific uptake of \[^{123}\text{I}\]FPCIT was greater than \[^{123}\text{I}\]ßCIT. (2) Whereas the striatal and occipital activity of \[^{123}\text{I}\]ßCIT was very stable over 18-27 h p.i. (less than 1%/h washout), the striatal and occipital activity of \[^{123}\text{I}\]FPCIT showed significant washout over 3-6 h p.i. (5%/8%/h). This was corroborated by plasma analysis showing elimination rates of 13%-20%/h for \[^{123}\text{I}\]FPCIT. (3) The striatal \(V_{p}^{*}\) values of \[^{123}\text{I}\]FPCIT gradually increased and became stable 3-6 h p.i., and the differences between the IPD patients and controls were greater with \[^{123}\text{I}\]FPCIT than with \[^{123}\text{I}\]ßCIT, consistent with the faster brain washout of \[^{123}\text{I}\]FPCIT and the resultant transient equilibrium state, which resulted in an overestimation of DAT density by \[^{123}\text{I}\]FPCIT in the controls. (4) The primary metabolite of \[^{123}\text{I}\]FPCIT is the carboxylic acid, similar to that of \[^{123}\text{I}\]ßCIT. (5) \[^{123}\text{I}\]FPCIT SPECT is sensitive to striatal DAT reductions in IPD patients and may provide useful data for clinical purposes. (6) \[^{123}\text{I}\]FPCIT may not provide the accurate DAT quantitation required for some clinical studies, as in the evaluation of IPD progression. However, the last point contradicts another study in 12 mildly affected IPD patients, concluding that \[^{123}\text{I}\]FPCIT SPECT can provide quantitative descriptors of presynaptic DAergic function comparable to those obtained with \[^{18}F\]FDOPA PET. In 10 IPD patients with decreased striatal uptake compared to the controls, age- corrective striatal distribution volume ratios correlated...
negatively with the UPDRS composite motor ratings.  
A profound reduction of uptake was shown with SPECT using [\(^{[12]}\)I]2-carboxyethyl-3-4(1-iodo-2-propanol)-3-
-3-yl)nortropane (\([12I]\)altropane or \([12I]\)IACFT) in the posterior putamen with relative sparing of the caudate nuclei in eight IPD patients compared to seven controls.  
These results are congruent with \([12I]\)altropane data in normal versus IPD human brain post mortem.  
The high selectivity and rapid striatal accumulation of \([12I]\)altropane may allow for accurate DAT quantification in less than 2 h and \([12I]\)altropane SPECT may be an additional effective clinical marker for IPD.

The question remains which marker would be more important to establish the status quo in vivo of the nigrostriatal pathway: one that assays the surviving neurons, like the markers discussed above, or a DA analogue, like \([18F]FDOPA\), that might be a better measure for the functional status of the surviving neurons. However, DA turnover is increased in animals with nigrostriatal lesions and in postmortem parkinsonian brain. As a result of this enhanced turnover, an increased proportion of radiometabolites may leave the brain of parkinsonian patients, exaggerating the deficits in these patients when measured with \([18F]FDOPA\). The assumption at present is that the number of DAT per nerve terminal remains constant in IPD, so that a ligand for the DAT can directly visualise the number of remaining nerve terminals. However, at present it cannot be excluded that as the loss of DAergic neurons reaches a critical threshold, the remaining neurons may compensate by decreasing the amount of DAT per terminal in order to maintain synaptic DA at a certain level. A PET study demonstrated that apomorphine decreased the striatal \([14C]L\)-DOPA influx rate in early IPD but not in advanced IPD patients. This suggests that the DAergic presynaptic inhibitory feedback regulation is intact in early IPD but diminished in advanced IPD patients.

Aging
Another question remains regarding the optimum age correction for comparison of striatal DAT in IPD patients versus controls. Aging is associated with a gradual degeneration of DAergic neurons and an accompanying loss of transmitter and transporter. A decrease of about 10%/decade has been described for DAT in postmortem samples, whereas PET with \([14C]\)β-CIT, \([12I]\)FP-CIT and \([12I]\)altropane in healthy volunteers showed comparable age-related striatal DAT declines of 7.6-9.6%/decade, whereas PET with \([14C]\)β-CIT, \([18F]\)FP-CIT and \([14C]d\)-three-methylphenydat showed declines of 4.6-7.7%/decade. However, the age-related DAT decline may be more rapid during young adulthood and less rapid throughout middle age so that nonlinear functions may be more optimal than linear functions to describe this. In addition, early IPD patients did not show any age-associated DAT decline with \([12I]\)FP-CIT SPECT, in contrast to healthy controls. These issues pose additional challenges for age correction in striatal DAT imaging.

Cortical dopamine transporters in IPD
In nine non-demented, non-depressed IPD patients, with mild marked side-to-side asymmetry in motor impairment, the clinical motor asymmetries significantly correlated in the clinically expected direction to asymmetries in neocortical (especially frontal) \([11C]\)nomifensine uptake. This suggests that monoamine neocortical denervation might play a direct role in motor impairment in IPD.

**Experimental therapies**

Firstly DAT and secondly D₂R PET or SPECT can be used in future to create homogeneous patient groups for clinical trials exploring both medical and surgical experimental therapies. In parkinsonian patients, possible additional damage in the connections forming the striato-thalamo-cortical circuit might occur. This is the clinical basis for therapies with NMDA receptor NR₂B subunit antagonists, AMPA receptor antagonists such as NBQX, alpha₂–adrenergic receptor agonists such as clonidine, and muscarinic receptor antagonists such as dextemidine, either alone or in combination, with or without apomorphine or other DA (D₂R) agonists. In a rat model, 6-OHDA was used to lesion the median forebrain bundle, resulting in a complete and irreversible destruction of the nigrostriatal pathway. When glial cell-line-derived neurotrophic factor (GDNF) was injected ipsilaterally above the substantia nigra and immediately before the unilateral 6-OHDA injection, it prevented both the 6-OHDA-induced reduction of DAT, measured by \([14C]\)IPCIT PET in the ipsilateral striatum, and the development of amphetamine-induced rotations. Therefore, GDNF may be useful for the treatment of IPD. One PET study was done in a unilateral IPD rat neurotransplantation model. In the lesioned striatum, the \([11C]β\)CFT binding ratio was reduced to 15-30% of the intact side. After DA neuronal transplantation, behavioral recovery occurred only after the \([11C]β\)CFT binding ratio had increased to 75-85% of the intact side. Therefore, DAT imaging could be a useful addition to placebo-controlled clinical trials evaluating the effect of fetal nigral transplantation in IPD.

**Conclusion**

Imaging of the presynaptic DAergic nigrostriatal neurons with SPECT or PET has been shown to be of value in detecting IPD at a very early (probably even presymptomatic) stage, in monitoring the severity of IPD and, combined with D₂R imaging, in differentiating parkinsonian syndromes. These techniques are being used in clinical trials to evaluate neuroprotective properties of medications that may inhibit the rate of progression of IPD and could also be used for such studies in other parkinsonian syndromes.

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References


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