J Neural Transm (2007) 114: 331–335
DOI 10.1007/s00702-006-0518-2
Printed in The Netherlands

Journal of Neural Transmission

Striatal FP-CIT uptake differs in the subtypes of early Parkinson's disease

J. Spiegel[1], D. Hellwig[2], S. Samnick[2], W. Jost[3], M.-O. Möllers[2], K. Fassbender[1], C.-M. Kirsch[2], U. Dillmann[1]

[1] Department of Neurology, and
[2] Department of Nuclear Medicine, Saarland University, Homburg/Saar, Germany
[3] Department of Neurology, Deutsche Klinik fur Diagnostik, Wiesbaden, Germany

Received March 11, 2006 / Accepted April 19, 2006 / Published online May 24, 2006

Summary In idiopathic Parkinson's disease (PD), a tremor-dominant type (TDT), an akinetic-rigid type (ART), and a mixed type (MT) are distinguished. We compared cerebral [I-123]FP-CIT SPECT in the PD subtypes (67 patients Hoehn and Yahr stage 1:26 with ART, 19 with MT, 22 with TDT). We measured the ratios putamen/occipital lobe binding and caudate nucleus/occipital lobe binding. Parkinsonian motor symptoms were quantified by UPDRS motor scale. In both putamen and caudate nucleus contralateral to the clinically affected body side TDT patients showed a significantly higher FP-CIT uptake than ART or MT patients (ANOVA; $p < 0.01$). Contralateral putamen and caudate nucleus FP-CIT uptake correlated significantly with severity of rigidity ($p < 0.01$) and hypokinesia ($p < 0.01$) but not with severity of resting or postural tremor ($p > 0.05$). The missing correlation between striatal FP-CIT uptake and tremor suggests, that further systems besides the nigrostriatal dopaminergic system may contribute to generation of parkinsonian tremor.

Keywords: Parkinson's disease, FP-CIT SPECT

Introduction

Previous SPECT studies revealed a reduced density of striatal dopamine transporters (DAT) in patients with idiopathic Parkinson's disease (PD; Asenbaum et al., 1998; Benamer et al., 2000a; Pirker et al., 2000; Spiegel et al., 2005). DAT SPECT investigates the presynaptic dopaminergic system by measuring the binding of DAT (Booij et al., 1998). There is a high sensitivity of DAT SPECT concerning the diagnosis of PD (Benamer et al., 2000a; Pirker et al., 2000). On the other hand, DAT SPECT tends to show reduced uptake in Parkinson's disease as well as other types of Parkinsonism such as PSP and MSA; therefore specificity of DAT SPECT regarding detection of atypical parkinsonian syndromes is rather low (Pirker et al., 2000; Kim et al., 2002). Today DAT SPECT is mainly used to differentiate between PD and essential tremor (Asenbaum et al., 1998; Benamer et al., 2000a). Striatal density of DAT, as quantified by DAT SPECT, correlates significantly with the UPDRS score (Ichise et al., 1999) and Hoehn and Yahr stage (Winogrodzka et al., 2001).

In PD, a tremor-dominant type (TDT), an akinetic-rigid type (ART), and a mixed type (MT) are distinguished due to predominant motor symptoms. Besides the predominant motor symptoms, there are further clinical differences between the different PD subtypes: TDT patients demonstrate slower rates of disease progression, lower impairment of cognitive functions – mostly obvious as executive dysfunction – and lower scores in the Beck depression inventory than non-tremor-dominant patients (Lewis et al., 2005). So far it is unclear, whether the PD subtypes are also different concerning nuclear medicine parameters. Therefore we now compared [I-123]FP-CIT SPECT in patients with different subtypes of PD. We examined patients at only one Hoehn and Yahr stage (stage 1) to optimize comparison of the different PD subtypes.

Patients and methods

Patients

The study involved 67 patients with idiopathic Parkinson's disease (PD), Hoehn and Yahr stage 1 (Hoehn and Yahr, 1967; 29 females, 38 males, age 37–78 years, 59 ± 11 years, mean $\pm$ SD, Table 1). Idiopathic PD was diagnosed according to the criteria of the UK Parkinson's Disease Society Brain Bank (Hughes et al., 1992). Two independent neurologists examined the patients. The motor part (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987) was used to assess the severity of

Correspondence: Dr. Jörg Spiegel, Department of Neurology, Saarland University, Kirrberger Straße, 66421 Homburg/Saar, Germany
e-mail: nejspi@uniklinik-saarland.de

Table 1. *Patients with idiopathic Parkinson's disease*

	Tremor-domin. type	Akinetic-rigid type	Mixed type
Patients			
N	$n = 22$	$n = 26$	$n = 19$
Females	$n = 9$	$n = 12$	$n = 8$
Males	$n = 13$	$n = 14$	$n = 11$
Age (mean ± SD)	60.1 ± 10.8	58.5 ± 9.9	58.0 ± 12.1
Disease duration (mean ± SD)	2.1 ± 1.5	2.0 ± 1.5	1.9 ± 1.1
UPDRS III (mean ± SD)	12 ± 4	11 ± 6	11 ± 4
Putamen uptake ratios			
Contral. FP-CIT (mean ± SD)	2.39 ± 0.77	1.82 ± 0.46	1.96 ± 0.58
Ipsilat. FP-CIT (mean ± SD)	2.61 ± 0.69	2.00 ± 0.49	2.20 ± 0.55
Contralat. FP-CIT normal	$n = 1$	$n = 0$	$n = 0$
Contralat. FP-CIT pathological	$n = 21$	$n = 26$	$n = 19$
Caudate nucleus uptake ratios			
Contral. FP-CIT (mean ± SD)	2.70 ± 0.54	2.22 ± 0.45	2.34 ± 0.54
Ipsilat. FP-CIT (mean ± SD)	2.92 ± 0.52	2.45 ± 0.44	2.59 ± 0.56
Contralat. FP-CIT normal	$n = 3$	$n = 1$	$n = 1$
Contralat. FP-CIT pathological	$n = 19$	$n = 25$	$n = 18$

All patients were at Hoehn and Yahr stage 1. Tremor-domin. type = tremor-dominance type. Age and disease duration are given in years. UPDRS III = motor part (part III) of the UPDRS scale, given in points. Contral. FP-CIT = contralateral FP-CIT uptake. Ipsilat. FP-CIT = ipsilateral FP-CIT uptake. Contralat. FP-CIT normal = number of patients with normal contralateral FP-CIT uptake. Contralat. FP-CIT pathological = number of patients with pathologically reduced contralateral FP-CIT uptake

disease. The scale was rated during an ''off'' phase (12 hour off drugs). The motor part of UPDRS scale was rated between 4 and 6 times within six months before SPECT examination and then averaged to exclude a bias due to temporary clinical changes.

Patients with any present or previous disease or medication, which might affect the FP-CIT uptake, were excluded. Therapy with selegiline was discontinued at least 18 hours before FP-CIT application to avoid interaction of its metabolites with FP-CIT at the dopamine transporter (Laruelle et al., 1993). Further anti-parkinsonian medication was continued during the SPECT examination. Informed consent was obtained from all patients prior to examination. The protocol was approved by the local ethics committee (Ethical Committee of General Medical Council, Saarland, Germany).

By means of motor part of UPDRS score patients were subdivided into PD subgroups of TDT, ART, and MT (Table 1): first we calculated a ''tremor score'' and a ''non-tremor score'' for each patient in a manner similar to Lewis et al. (2005): the tremor score was derived from the sum of UPDRS items 20 (*tremor at rest*) and 21 (*action or postural tremor of hands*) divided by 7 (the number of single sub-items [for each body region if separated] included). The non-tremor score was derived from the sum of UPDRS items 18 (*speech*), 19 (*facial expression*), 22 (*rigidity*), 27 (*arising from chair*), 28 (*posture*), 29 (*gait*), 30 (*postural stability*) and 31 (*body bradykinesia and hypokinesia*) divided by 12 (the number of single sub-items [for each body region if separated] included). The patient was classified as tremor-dominant type, if the tremor score was at least twice the non-tremor score. Vice versa, the patient was classified as akinetic-rigid type, if the non-tremor score was at least twice the tremor score. The remaining patients, in whom the tremor and non-tremor score differed by less than factor 2, were classified as mixed type. TDT, ART and MT patients were not significantly different concerning age, duration of disease, or motor part of the UPDRS (ANOVA, $p > 0.05$).

In a second step, we calculated the correlation between striatal FP-CIT uptake (contralateral to the clinically affected body side) and the severity of parkinsonian cardinal symptoms tremor, hypokinesia, and rigidity over all patients. We were interested, whether the severity of clinical cardinal symptoms correlates with putamen or caudate nucleus FP-CIT uptake. Furthermore, we performed this second step, since there is a continuous spectrum of severity of tremor, hypokinesia, and rigidity across the cohort; thus the subdivision into TDT, MT and ART patients might be too general under some circumstances. The quantification of the clinical feature *resting tremor* derived from UPDRS item 20 (*tremor at rest*), *postural tremor* from item 21 (*action or postural tremor of hands*), *rigidity* from item 22 (*rigidity*), *hypokinesia* from the items 18 (*speech*), 19 (*facial expression*), 27 (*arising from chair*), 28 (*posture*), 29 (*gait*) and 31 (*body bradykinesia and hypokinesia*).

Data acquisition

Cerebral SPECT imaging was performed with a triple-head gamma camera (Siemens Multispect, MS 3). 4 hours following thyroid gland blocking and intravenous injection of iodine-123 ioflupane (185 ± 10 MBq, specific activity: 580–1040 GBq/mg, DaTscan®, Amersham Cygne, Braunschweig, Germany) cerebral SPECT images were obtained. The triple-head gamma camera was equipped with low-energy high-resolution collimators using a 20% energy window centered on the 159 keV photo-peak of iodine-123. System resolution for iodine-123 was 7.5 mm full width at half maximum (FWHM) at 10 cm distance. During SPECT acquisition 120 projections at 3° steps were recorded over 50 seconds per view in a 128×128 matrix. Transaxial images were reconstructed using an iterative algorithm (OSEM, 6 subsets, 4 iterations) including contour-based attenuation correction ($\mu = 0.1/\text{cm}$) and post-reconstruction filtering (Butterworth 4^{th} order, cutoff 1.0/cm). Registration and semi quantitative analysis were performed with a workstation (HERMES, Nuclear Diagnostics, Stockholm, Sweden) and a software named BRASS (Nuclear Diagnostics, Stockholm, Sweden). The putamen, caudate nucleus and occipital lobe binding of [I-123]FP-CIT was assessed semiquantitatively by a regions of interest (ROI) technique and compared with a control group. The ROI's included 689 pixels (according volume = 5.5 cm^3) for each putamen, 524 pixels (according volume = 4.2 cm^3) for each caudate nucleus, and 9008 pixels (according volume = 72 cm^3) for both occipital cortices together. We regarded a small central area

within each nucleus and did not consider the whole nucleus to avoid partial volume and resolution effects. We calculated the ratio *putamen/occipital lobe binding* and the ratio *caudate nucleus/occipital lobe binding*. The control group consisted of 19 age-matched healthy volunteers without any present or previous neurological or psychiatric disease (age 38–76 years, 59 ± 11 years, mean ± SD). In these volunteers the ratio *putamen/occipital lobe binding* was 3.44 ± 0.35 (resulting norm value = mean −2 SD: ≥2.74) for the right putamen and 3.52 ± 0.36 (≥2.80) for the left putamen. The ratio *caudate nucleus/occipital lobe binding* was 3.67 ± 0.36 (≥2.95) for the right caudate nucleus and 3.67 ± 0.37 (≥2.93) for the left caudate nucleus. Putamen or caudate nucleus FP-CIT binding was considered pathological when 1) the absolute tracer accumulation was below these absolute norm values or 2) the side – to – side difference (affected versus unaffected striatal area) was above Δ0.15 (mean + 2 SD). Clinical examination including clinical scores and FP-CIT SPECT examination were performed independently by physicians, who were blinded to the results of the other examination.

Statistical analysis

ANOVA was used for group comparison of nuclear medicine data, since all nuclear medicine data were normally distributed. For correlations Pearson's correlation was used in case of normally distributed data, Spearman's correlation in case of not normally distributed data. For correlations between single UPDRS items and FP-CIT uptake we used Spearman's correlation, since the single UPDRS items represent ordinal data on a 4-point scale.

Results

FP-CIT uptake in the putamen

In the putamen contralateral to the clinically affected body side (= contralateral putamen), TDT patients showed a

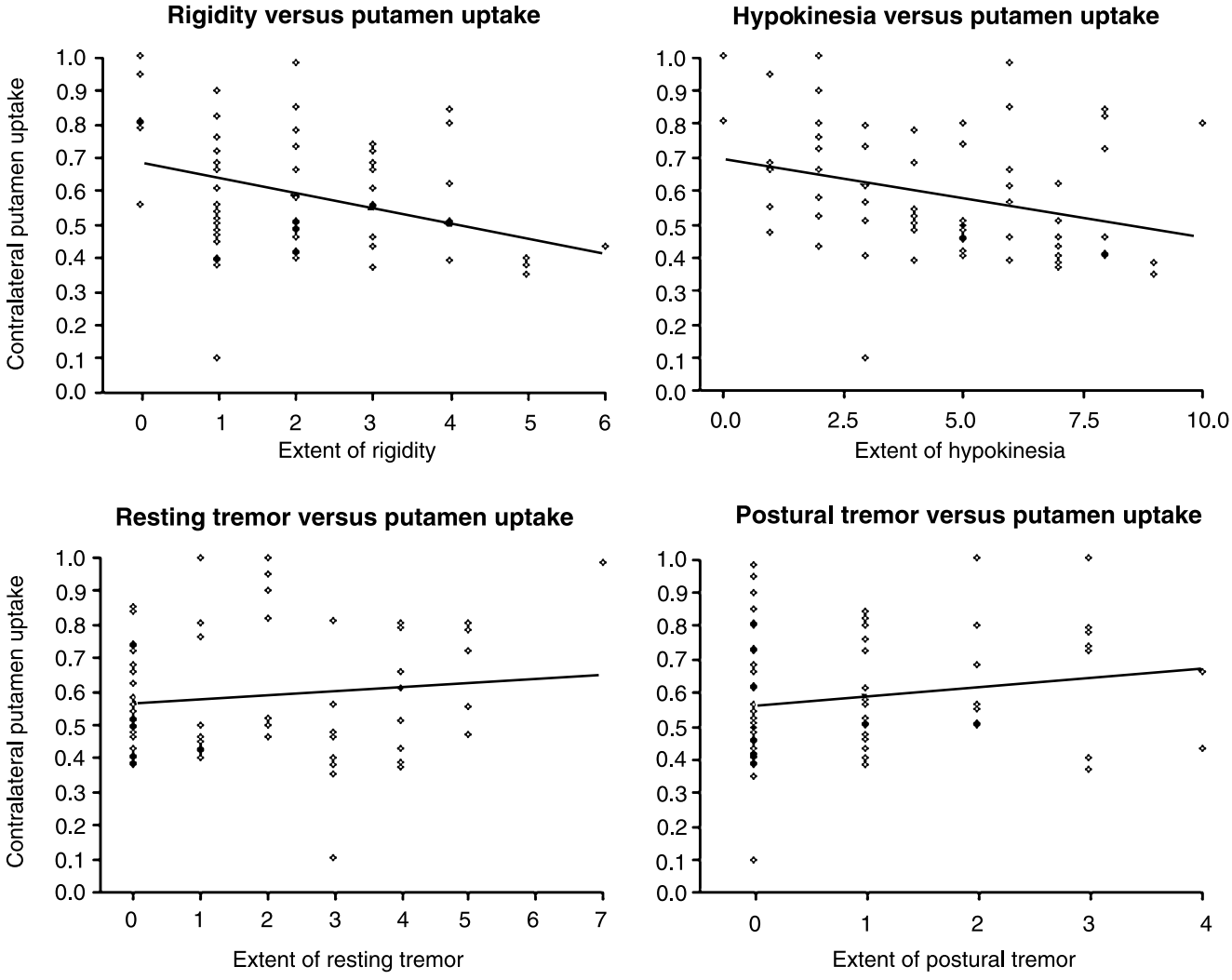

Fig. 1. Correlation between contralateral putamen uptake and clinical symptoms. Each of the 67 patients is represented by one circle; the regression is symbolized by an inserted straight line. Contralateral putamen uptake was quantified by the binding-ratio putamen/occipital lobe and related to the according mean value of the control group (age-matched healthy volunteers); the latter was put on the level of 1 (= 100%). In two patients FP-CIT SPECT was pathological due to a pathologically increased side-to-side difference of putamen FP-CIT uptake. Extent of clinical parameters (rigidity, hypokinesia, resting tremor and postural tremor) was quantified by the sum of the according UPDRS items, for which both body sides – clinically affected body side as well as clinically unaffected body side – were considered

significantly higher FP-CIT uptake than ART or MT patients (ANOVA; $p<0.01$; $F=5.41$; $R^2=0.15$; Table 1). Considering our norm values the contralateral putamen uptake was pathologically reduced in 21 of 22 TDT patients and all ART and MT patients.

There were similar findings in the ipsilateral putamen (Table 1); TDT patients revealed a significantly higher uptake than ART or MT patients (ANOVA; $p<0.01$; $F=6.48$; $R^2=0.17$). There were no significant differences between ART and MT patients concerning binding ratios in the contra- or ipsilateral putamen, or in the ipsi- and contralateral putamen pooled together (pooled data, $p=0.51$; unpaired *t*-test).

Over all 67 patients, FP-CIT uptake in the contralateral putamen correlated significantly with the extent of rigidity ($r=-0.34$; $p<0.01$; $n=67$; Spearman's correlation; Fig. 1) and hypokinesia ($r=-0.36$; $p<0.01$; $n=67$), but not with the extent of resting tremor ($r=+0.08$; $p=0.54$; $n=67$) or postural tremor ($r=+0.14$; $p=0.24$; $n=67$). Contralateral putamen uptake did not significantly correlate with age or disease duration ($p>0.05$; multiple regression analysis).

FP-CIT uptake in the caudate nucleus

In the contralateral caudate nucleus TDT patients showed a significantly higher FP-CIT uptake than ART or MT patients (ANOVA; $p<0.01$; $F=5.54$; $R^2=0.15$; Table 1). Following our norm values the contralateral caudate nucleus uptake was considered pathological in 19 of 22 TDT, 25 of 26 ART, and 18 of 19 MT patients.

Similar findings were disclosed in the ipsilateral caudate nucleus; TDT patients revealed a significantly higher uptake than ART or MT patients (ANOVA; $p<0.01$; $F=5.58$; $R^2=0.15$). There were no significant differences between ART patients and MT patients concerning binding properties in the contra- or ipsilateral caudate nucleus, or the ipsi- and contralateral caudate nucleus pooled together (pooled data, $p=0.22$; unpaired *t*-test).

Over all 67 patients, FP-CIT uptake in the contralateral caudate nucleus correlated significantly with severity of rigidity ($r=-0.45$; $p<0.001$; $n=67$) and hypokinesia ($r=-0.48$; $p<0.0001$; $n=67$) but not with severity of resting tremor ($r=+0.05$; $p=0.66$; $n=67$) or postural tremor ($r=+0.10$; $p=0.43$; $n=67$). There was no significant correlation between contralateral nucleus caudate uptake and age or disease duration ($p>0.05$; multiple regression analysis).

In all subgroups (TDT, ART and MT patients) putamen uptake was significantly lower than caudate nucleus uptake ($p<0.0001$ each; Student's paired *t*-test). The relation between lower putamen uptake and relatively higher caudate nucleus uptake (quotient [*contralateral caudate nucleus uptake ratio*/*contralateral putamen uptake ratio*]) was similar and not significantly different between TDT, ART and MT patients (ANOVA; $p>0.05$).

Discussion

In the present study we investigated and compared FP-CIT uptake in four striatal areas: putamen and caudate nucleus contralateral to the clinically affected body side (= contralateral putamen and contralateral caudate nucleus) as well as putamen and caudate nucleus ipsilateral to the clinically affected body side (= ipsilateral putamen and ipsilateral caudate nucleus). TDT patients revealed a significantly higher FP-CIT uptake in all four striatal areas than ART or MT patients at the same Hoehn and Yahr stage. In a further step, we examined the correlation between striatal FP-CIT uptake and severity of parkinsonian clinical cardinal symptoms over all patients: FP-CIT uptake in both contralateral putamen and caudate nucleus correlated significantly with severity of hypokinesia and rigidity but not with severity of resting tremor or postural tremor. Comparing putamen FP-CIT uptake versus caudate nucleus FP-CIT uptake, putamen uptake was significantly more impaired than caudate nucleus uptake, in accordance with previous DAT imaging studies (Asenbaum et al., 1998; Benamer et al., 2000b). The relation between lower putamen uptake and relatively higher caudate nucleus uptake was similar and not significantly different between TDT, ART and MT patients.

As mentioned above, we found a significantly higher striatal FP-CIT uptake in TDT patients than in ART or MT patients. The reason for this significantly differing striatal FP-CIT uptake in the subtypes of PD remains yet unclear. It could be speculated that manifestation of tremor is earlier noticed than stiffness of movements (frequently ascribed to aging or arthritis). The conclusion would be that TDT patients are detected at an earlier stage of disease than ART or MT patients. Hence the striatal FP-CIT binding would be less affected in TDT patients than in ART or MT patients. Two facts, obtained from our study, contradict this assumption and show that our TDT patients belonged to the same stage of disease as our ART and MT patients: 1) if the TDT patients were at an earlier stage of disease due to an earlier diagnosis, lower values of UPDRS/motor part in TDT patients than in ART or MT patients would be expected. In our study, TDT patients revealed – on average – slightly (not significantly) higher scores of UPDRS/motor part than ART or MT patients. 2) If TDT patients would be earlier diagnosed because of the specific symptom tremor, it could be concluded that some MT patients with tremor should be detected in an earlier stage, too. Hence the MT patients

should exhibit a higher FP-CIT uptake than the ART patients. In our study the MT patients had nearly the same mean value for ipsi- and contralateral FP-CIT uptake as the ART patients. Due to the above observations the TDT patients were in the same stage of disease as the ART and MT patients.

As a second result of our study, contralateral FP-CIT uptake correlated significantly with the clinical symptoms rigidity and hypokinesia but not with the clinical symptom tremor. Already previous DAT imaging studies (Seibyl et al., 1995; Rinne et al., 1999; Benamer et al., 2003; Pirker, 2003) reported a significant correlation of putamen and caudate FP-CIT uptake with severity of akinetic-rigid features but not with tremor in PD. Fluorodopa-PET studies (Otsuka et al., 1996; Vingerhoets et al., 1997) also described a significant correlation of nigrostriatal deficit with bradykinesia and rigidity but not with tremor. This missing correlation between nigrostriatal dopaminergic deficits and severity of tremor suggests, that other neural systems – apart from the nigrostriatal dopaminergic system – may contribute to generation of parkinsonian tremor. There are further significant differences between TDT and ART patients: TDT patients typically demonstrate slow rates of disease progression, no or less cognitive impairment, and an absence of depressive symptoms (Lewis et al., 2005). In contrast, non-tremor-dominant patients exhibit cognitive impairment mostly demonstrated by executive dysfunction, significant depression scoring >9 in the Beck depression inventory, and a more rapid disease progression (Lewis et al., 2005). Ages at disease onset are markedly differently distributed between TDT, ART, and MT patients. A positive family history for Parkinson's disease appears significantly more often in TDT than in MT or ART patients with later onsets of disease (Korchounov et al., 2004).

In summary, TDT patients Hoehn and Yahr stage 1 show a significantly higher striatal FP-CIT uptake than ART or MT patients at the same stage of disease. Further systems besides the nigrostriatal dopaminergic system seem to be involved in generation of parkinsonian tremor.

References

Asenbaum S, Pirker W, Angelberger P, Bencsits G, Pruckmayer M, Brücke T (1998) [123I]β-CIT SPECT in essential tremor and Parkinson's disease. J Neural Transm 105: 1213–1228

Benamer HTS, Patterson J, Grosset DG (2000a) Accurate differentiation of parkinsonian and essential tremor using visual assessment of [123I]-FP-CIT-SPECT imaging: the [123I]-FP-CIT study group. Mov Disord 15: 503–510

Benamer HTS, Patterson J, Wyper DJ, Hadley DM, MacPhee GJA, Grosset DG (2000b) Correlation of Parkinson's disease severity and duration with 123I-FP-CIT SPECT striatal uptake. Mov Disord 15: 692–698

Benamer HTS, Oertel WH, Patterson J, Hadley DM, Pogareff O, Hoffken H, Gerstner A, Grosset DG (2003) Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: Part 1. baseline and 3-month observations. Mov Disord 18: 977–984

Booij J, Sokole EB, Stabin MG, Janssen AGM, de Bruin K, van Royen EA (1998) Human biodistribution and dosimetry of [123I]FP-CIT: a potential radioligand for imaging of dopamine transporters. Eur J Nucl Med 25: 24–30

Fahn S, Elton RL and members of the UPDRS Development Committee (1987) Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M (eds) Recent developments in Parkinson's disease. Macmillan Healthcare Information, Florham Park, HJ, pp 153–164

Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17: 427–442

Hughes A, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55: 181–184

Ichise M, Kim YJ, Ballinger JR, Vines D, Erami SS, Tanaka F, Lang AE (1999) SPECT imaging of pre- and postsynaptic dopaminergic alterations in L-dopa untreated Parkinson's disease. Neurology 52: 1206–1214

Kim YJ, Ichise M, Ballinger JR, Vines D, Erami SS, Tatschida T, Lang AE (2002) Combination of dopamine transporter and D2 receptor SPECT in the diagnostic evaluation of PD, MSA and PSP. Mov Disord 17: 303–312

Korchounov A, Schipper HI, Preobrazhenskaya IS, Kessler KR, Yakhno NN (2004) Differences in age at onset and familial aggregation between clinical types of idiopathic Parkinson's disease. Mov Disord 19: 1059–1064

Laruelle M, Baldwin RM, Malison RT, Zea-Ponce Y, Zogbhi SS, Al-Tikriti MS, Sybirska EH, Zimmermann RC, Wisniewski G, Neumeyer JL (1993) SPECT imaging of dopamine and serotonin transporters with [123I]ß-CIT: pharmacological characterization of brain uptake in non-human primates. Synapse 13: 295–309

Lewis SJG, Foltynie T, Blackwell AD, Robbins TW, Owen AM, Barker RA (2005) Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J Neurol Neurosurg Psychiatry 76: 343–348

Otsuka M, Ichiya Y, Kuwabara Y, Hosokawa S, Sasaki M, Yoshida T, Fukumura T, Masuda K, Kato M (1996) Differences in the reduced 18F-Dopa uptakes of the caudate and the putamen in Parkinson's disease: correlations with the three main symptoms. J Neurol Sci 136: 169–173

Pirker W, Asenbaum S, Bencsits G, Prayer D, Gerschlager W, Deecke L, Brucke T (2000) [123I]beta-CIT SPECT in multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration. Mov Disord 15: 1158–1167

Pirker W (2003) Correlation of dopamine transporter imaging with parkinsonian motor handicap: how close is it? Mov Disord 18 [Suppl 7]: S43–S51

Rinne JO, Ruottinen H, Bergman J, Haaparanta M, Sonninen P, Solin O (1999) Usefulness of a dopamine transporter PET ligand [(18)F]beta-CFT in assessing disability in Parkinson's disease. J Neurol Neurosurg Psychiatry 67: 737–741

Seibyl JP, Marek KL, Quinlan D, Sheff K, Zoghbi S, Zea-Ponce Y, Baldwin RM, Fussell B, Smith EO, Charney DS (1995) Decreased single photon emission computed tomography [123I]ß-CIT striatal uptake correlates with symptom severity in Parkinson's disease. Ann Neurol 38: 589–598

Spiegel J, Mollers MO, Jost WH, Fuss G, Samnick S, Dillmann U, Becker G, Kirsch CM (2005) FP-CIT and MIBG scintigraphy in early Parkinson's disease. Mov Disord 20: 552–561

Vingerhoets FJ, Schulzer M, Calne DB, Snow BJ (1997) Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? Ann Neurol 41: 58–64

Winogrodzka A, Bergmans P, Booij J, van Royen EA, Janssen AGM, Wolters EC (2001) [123I]FP-CIT SPECT is a useful method to monitor the rate of dopaminergic degeneration in early-stage Parkinson's disease. J Neural Transm 108: 1011–1019