Clinical impact of diagnostic SPET investigations with a dopamine re-uptake ligand

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Abstract. The diagnosis of Parkinson's disease is based on clinical features with pathological verification. However, autopsy has been found to confirm a specialist diagnosis in only about 75% of cases. Especially early in the course of the disease, the clinical diagnosis can be difficult. Imaging of presynaptic dopamine transporters (DAT receptors) has provided a possible diagnostic probe in the evaluation of Parkinson's disease. The cocaine analogue [^{123}I]-2-β-carboxymethoxy-3-β(4-iodophenyl)tropane ([^{123}I]-β-CIT) is one of several radioligands that have been developed for single-photon emission tomography (SPET). The purpose of this study was to evaluate the impact of [^{123}I]-β-CIT SPET on the diagnosis and clinical management of patients with a primary, tentative diagnosis of parkinsonism. We undertook a retrospective evaluation of the clinical records of 90 consecutive patients referred to [^{123}I]-β-CIT SPET from the neurological department, Bispebjerg Hospital. In 58 subjects the scans revealed altered tracer uptake consistent with Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. A significant change in the management or treatment because of the scan was found in 25 patients (28%). The sensitivity of the examination was 97% and the specificity 83%. In conclusion, a significant clinical impact of DAT receptor SPET imaging was found. DAT receptor imaging is a useful diagnostic probe in patients with a possible diagnosis of parkinsonism.

Keywords: Single-photon emission tomography – Dopamine transporter – Parkinson's disease – Differential diagnosis

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Introduction

Parkinson's disease (PD) is a neurodegenerative progressive disease. The age of onset is usually between 50 and 79 years, and the prevalence in the age group over 65 years is about 1.6% [1]. The diagnosis of idiopathic PD is based on clinical findings. A definite diagnosis is provided by neuropathological microscopy showing neuronal cell loss in substantia nigra and Lewy bodies in some of the remaining neurones.

A patient with the clinical features of parkinsonism (i.e. rigidity, bradykinesia and tremor) that respond well to dopaminergic medication has a probable clinical diagnosis of PD [2]. Parkinsonism, however, can also be found in a number of other diseases, e.g. "parkinsonism plus" [(multiple system atrophy (MSA), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP)], and essential tremor. Secondary parkinsonism can be induced by vascular events, hydrocephalus, drugs, infection, trauma or toxins [3].

Clinically it can be difficult to distinguish between these different forms of parkinsonism [4]. Some clinicopathological studies have shown that autopsy confirms a specialist diagnosis in only 76% of cases [5, 6]. A correct clinical diagnosis, however, is important for adequate treatment and prognosis. Especially the emergence of possible neuroprotective drugs [7] has prompted a search for early markers of PD [8].

Imaging of presynaptic dopamine transporters (DAT receptors) has provided a possible diagnostic probe in the evaluation of PD. The cocaine analogue [^{123}I]-2-β-carboxymethoxy-3β(4-iodophenyl)tropane ([^{123}I]-β-CIT) is one of several radioligands that have been developed for single-photon emission tomography (SPET). [^{123}I]-β-CIT has been shown to have high affinity for DAT receptors in the striatum [9]. A number of studies have shown a correlation between [^{123}I]-β-CIT uptake in the striatum and symptom severity (UPDRS, H&Y) [10, 11] and age [12]. Studies of hemiparkinsonian patients [13] have shown possible pre-symptomatic changes, in accordance with the 50%–80% loss of nigral neurones preceding

parkinsonian symptoms. DAT receptor imaging has been shown to differentiate parkinsonism with degenerative changes in the striatum (PD and parkinsonism plus) from other forms of parkinsonism, tremor or normal controls [14, 15]. Previously, only one report regarding the overall clinical benefit of imaging DAT receptors has been published [16].

In this report we focus on the clinical impact of DAT receptor SPET scanning. Clinical impact was registered as improvement in the ability to make a diagnosis shortly after the scan and to adjust adequately the management or treatment in a population of patients referred from specialists in neurology working at a movement disorder clinic.

Materials and methods

Subjects. Ninety patients examined and treated at the movement disorder clinic at the Department of Neurology, Bispebjerg Hospital, Copenhagen, were referred to [^{123}I]-β-CIT SPET from 1997 to 2000. The referring physician had classified the patients according to generally established clinical criteria (Tables 1, 2). The mean age was 59 years (mean±SD 14 years; range 21–82). Fifty-six patients were males and 34, females. In 80 patients, symptoms of parkinsonism were reported at referral. The duration of disease and the effect of medication are listed in Table 3. Immediately after each scan the result of the investigation was submitted to the neurologist in charge of the patient.

Table 1. Suggested diagnoses at the time of referral[a]

Diagnosis at the time of referral	No. of patients
Probable PD	16
Possible PD	41
Possible parkinsonism plus	19
Possible drug-induced parkinsonism	4
Possible dystonia	6
Probable essential tremor	4
Total	90

[a] The diagnosis at referral was stated by the referring doctor in accordance with the general diagnostic criteria used in the department Probable PD, Clinically diagnosed Parkinson's disease; possible PD: clinically possible Parkinson's disease

Retrospective evaluation. The final information on outcome and most likely diagnosis after months to years of observation was obtained retrospectively from the clinical records by one specialist in neurology (L.M.W.) blinded to the result of the scan (Table 4). The time of evaluation was autumn 2001. The diagnoses were based on generally established clinical criteria [17, 18]. The most important criteria have been listed briefly in Table 2. In 22 patients the observation period ended before the time of this evaluation because of referral to other departments or the general practitioner, or because of death.

A clinical impact of the scan diagnosis was noted when it caused a change in treatment, management or diagnosis. When confirmation of the referral diagnosis was established, this was not in itself considered to represent a clinical impact; however, sometimes this establishment of the diagnosis led to a change in management or medication, which was then noted as a clinical impact of the result of the scan.

SPET protocol. Patients received 200 mg of sodium perchlorate i.v. prior to the radiotracer injection in order to block uptake of iodine-123 in the thyroid. Subsequently they received 120 MBq [^{123}I]-β-CIT i.v. The SPET scan was performed 20 h after the [^{123}I]-β-CIT injection, when a steady state had been reached.

Image acquisition was carried out with a Tomomatic 232, head-dedicated SPET scanner in the first 72 patients. In 18 patients the image acquisition was carried out with a Marconi PRISM 3000XP triple-head gamma camera with ultra-high-resolution, fan-beam collimators. SPET acquisitions were performed using a 360º orbit for each collimator. A gadolinium-153 pin source

Table 2. Criteria for the diagnosis at the time of evaluation[a]

Parkinson's disease	Positive criteria	Bradykinesia and rigidity and/or rest tremor
	Supportive signs	A good and sustained response to levodopa (anti-parkinsonian medication), unilateral onset, asymmetry of symptoms, rest tremor, slow progression of the disease
Possible parkinsonism plus	MSA	Cerebellar symptoms (ataxia, falls) and/or pyramidal signs (hyperreflexia, extensive plantar response), autonomic dysfunction (impotence, urinary dysfunction). A poor response to levodopa
	PSP	Early unsteadiness and falls, downgaze palsy, early memory impairment. A poor response to levodopa
	CBD	Cortical symptoms such as apraxia, myoclonus, alien limb or pyramidal signs
Cerebrovascular	Atypical parkinsonism, especially lower body parkinsonism. Vascular changes on CT or MRI	
Dystonia	A presentation of repetitive muscle spasms or twisting, either in one muscle group or generalised. Possibly tremor	
Essential tremor	A presentation of mainly postural or action tremor. No rigidity or bradykinesia	

[a] Generally established diagnostic criteria were used; for a description, see Sawle 1999. A diagnosis of PD was based on British Brain Bank Criteria. Possible parkinsonism plus was noted when the patients had symptoms in accordance with one of the following three diseases: multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD)

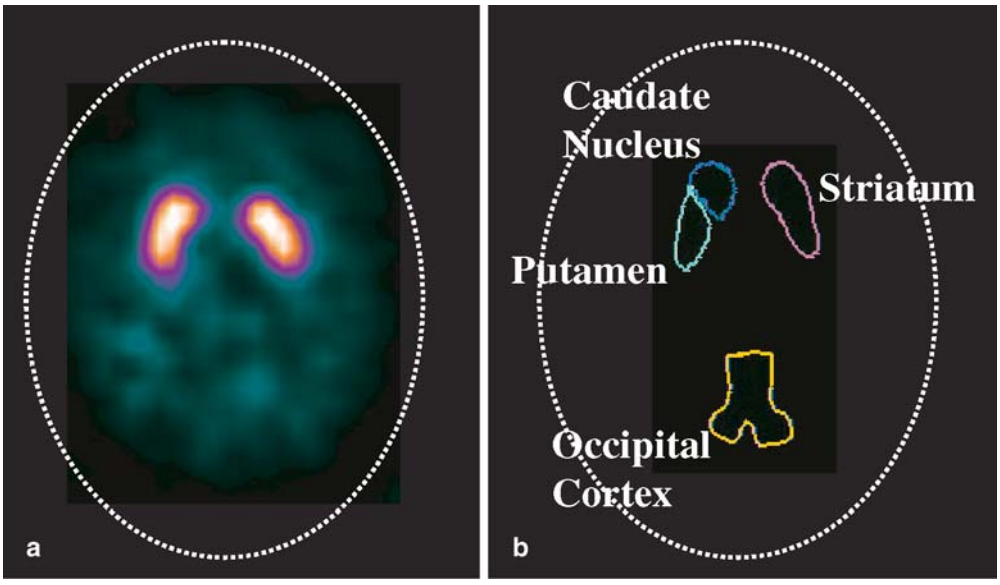

Fig. 1. A [^{123}I]-β-CIT SPET scan from a patient with normal uptake. The acquisition was performed using the PRISM scanner and yielded 4-mm slices of the brain. For calculation of the uptake of [^{123}I]-β-CIT, the three slices with the highest activity were added and analysed. The striatal uptake was calculated in each case. **B** A standard region of interest (ROI) template was used in the two scanners. The template with ROIs was based on previously obtained CT scans. The template used in the Tomomatic was adjusted slightly in order to produce equivalent results in the PRISM. In this figure the four different regions are shown. On both the left and the right side, the regions striatum, caudate nucleus and putamen were placed. The occipital cortex was used as a region for calculation of non-specific uptake as it is considered to be devoid of dopaminergic receptors. The following uptake ratios were calculated: (1) striatum/occipital cortex, (2) caudate nucleus/putamen and (3) putamen/occipital cortex

Table 3. The effect of medication and the duration of disease in patients with symptoms of parkinsonism at referral

Diagnosis	No.	Duration of disease (years)	Effect of anti-parkinsonian medication	No effect of anti-parkinsonian medication	Unknown effect of anti-parkinsonian medication
Probable PD	16	13.5	15	0	1 patient: questionable effect
Possible PD	41	5.9	13	12	9 patients: no anti-parkinsonian medication; 5 patients: insufficient dose; 2 patients: no information
Possible parkinsonism plus	19	3.4	1	11	5 patients: no anti-parkinsonian medication; 1 patient: insufficient dose; 1 patient: no information
Possible drug-induced parkinsonism	4	4.5	2	0	1 patient: no anti-parkinsonian medication; 1 patient: insufficient dose

was used for simultaneous transmission scans. Image processing was performed using iterative reconstruction with scatter and non-uniform attenuation correction. The iterative algorithm OS-EM (ordered subsets-expectation maximisation) was used.

Data analysis. All scans were interpreted immediately after the investigation by the same specialist in nuclear medicine (L.F.). The clinical replies consisted of a visual interpretation as well as a quantified dataset.

The specific uptake was calculated in each case. A standard ROI template was used (Fig. 1). The template was based on previously obtained computed tomography (CT) scans. The template used for interpreting the scans on the Tomomatic SPET scanner was adjusted to provide similar results for both SPET scanners (cross-correlation). The region used for the calculation of the specific uptake was the striatum, which consists of the caudate nucleus and the putamen, on the left and right sides of the brain. The region chosen for the calculation of non-specific uptake was the occipital cortex, since it is considered to be devoid of DAT receptors. The regions were placed on a 12-mm slice of the brain representing the highest uptake of [^{123}I]-β-CIT. The uptake was calculated as the ratio between the uptake in the striatum and that in the occipital cortex.

The criteria for a normal scan were based on data from the literature [19, 20]. A reduction in the specific striatal [^{123}I]-β-CIT uptake was considered abnormal. Asymmetrical uptake and/or an

increased ratio of caudate nucleus to putaminal uptake was also considered abnormal. In a few cases it was difficult to reach a clear-cut conclusion at the time of the scan, and the result was defined as "borderline changes". Some of these scans presented normal striatal uptake, but with abnormal right-left asymmetry or a high ratio of caudate nucleus to putaminal uptake.

Results

The mean of the left and right striatal uptake of [^{123}I]-β-CIT in the different referred groups is shown in Fig. 2. The group with known PD had a marked reduction of [^{123}I]-β-CIT uptake compared with the other groups, in accordance with the established clinical diagnosis of PD (Table 3). In addition, in this group all the scans were pathological, in accordance with the longer duration of disease in these patients. The group of patients with dystonia had normal uptake. The other groups had variable uptake, as illustrated by both normal and pathological scan diagnoses. Based on the read-out of the [^{123}I]-β-CIT SPET scans and the calculated ratios, the patients were classified with the terms: "PD", "borderline changes" or "normal". The relation between the mean of the left and right striatal uptake of [^{123}I]-β-CIT and the age of the patients is shown in Fig. 3. The age-related reduction was different in the group with the scan result "normal" and that with the scan result "PD": the age-related decay in DAT receptors seemed larger in the normal group than in the PD group. For the scans with reduced striatal uptake (i.e. the patients with a scan diagnosis of PD or parkinsonism plus), the ratio of striatal uptake to uptake in the occipital cortex is depicted in Fig. 4 as a function of the duration of the disease. A higher uptake, but a large variability, can be seen for short disease duration.

The referral diagnoses of the patients are shown in Table 1. For each of these seven groups the relation to the scan diagnoses was noted (Table 4). Ninety patients were examined; 60 scans had reduced uptake in accordance with PD or parkinsonism plus, 25 scans were normal, and five scans had borderline changes.

The result of the [^{123}I]-β-CIT SPET investigations could be seen to correlate well with the later retrospective clinical diagnoses (Table 4). Among the 60 patients with a scan diagnosis of PD, three were classified as having a diagnosis other than PD or PP at the time of evaluation (false positives). Of the 25 patients with normal scan results, two were classified as having a diagnosis of either PD or PP at the time of evaluation (false negatives).

When the five investigations with "borderline changes" were excluded, [^{123}I]-β-CIT SPET had a sensitivity of 97% and a specificity of 88%. The five investigations with borderline changes were re-analysed by an investigator blinded to the clinical diagnosis at the time of evaluation (Table 4). When they were included in the analyses on the basis of the most likely diagnosis, the sensitivity was 97% and the specificity, 83%.

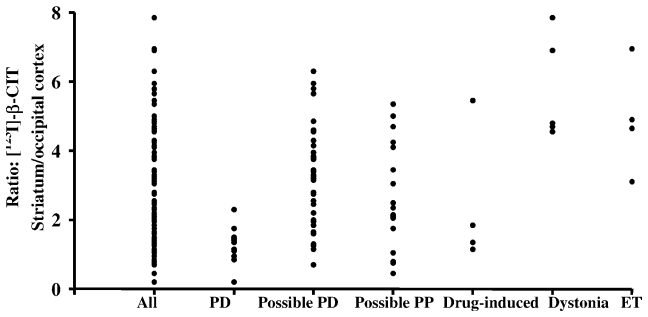

Fig. 2. The specific uptake in the striatum in the seven different referred groups of patients. *PD*, Parkinson's disease, *PP*, parkinsonism plus; *Drug-induced*, parkinsonism possibly caused by previous medicamentous treatment; *ET*, essential tremor. The group with clinically definite PD had very low striatal uptake, while all the patients in the group with dystonia had normal uptake. The groups with possible PD or parkinsonism plus showed a wide range of uptake: normal uptake was observed in 41 of these 60 patients and reduced uptake in 19. This wide range also in part reflects variation due to age

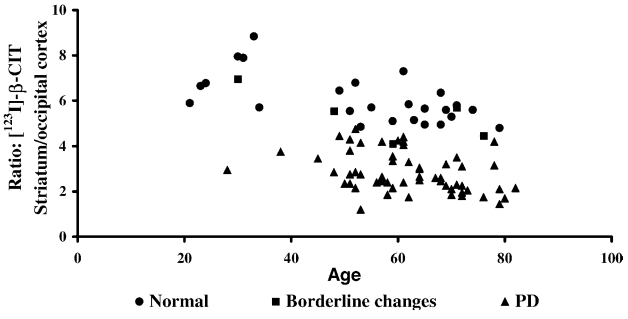

Fig. 3. Mean striatal uptake of [^{123}I]-β-CIT in the three groups of patients classified as "PD", "borderline changes" or "normal" on the basis of the read-out of the [^{123}I]-β-CIT SPET scans and the calculated ratios. Reduced striatal uptake as a function of age was found. The reduction seemed most marked in the group without pathologically reduced striatal uptake

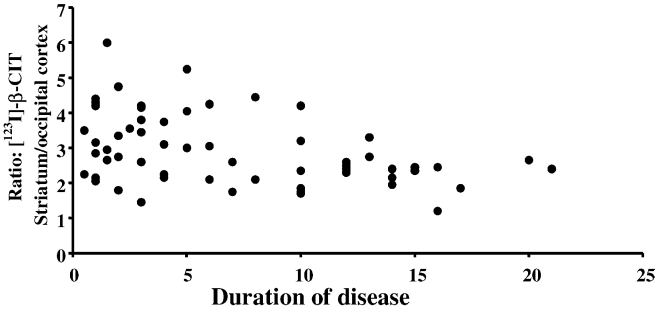

Fig. 4. Ratio of striatal uptake to uptake in the occipital cortex as a function of the duration of disease for patients in whom scans showed reduced striatal uptake (i.e. those with a scan diagnosis of PD or parkinsonism plus). No significant correlation was found

Table 4. Summary of the relation between the referral diagnosis, the scan diagnosis and the clinical diagnosis at the time of evaluation[a]

Diagnosis at time of referral (1997–2000)		Scan diagnosis (1997–2000)		Clinical diagnosis at time of evaluation (autumn 2001)	
PD	16	PD	16	PD	15
				Pplus	1
Possible PD	41	Normal	13	Dystonia	4
				ET	4
				PD	1
				Hydrocephalus	1
				Cerebrovascular	1
				Atypical depression	1
		PD	26	PD	23
				Pplus	1
				Primary dementia	1
				Cerebrovascular	1
		Borderline	2	Dystonia	1
				Cerebrovascular	1
Possible Pplus	19	Normal	3	Dystonia	1
				Pplus	1
				Autonomic dysfunction	1
		PD	15	PD	5
				Pplus	9
				Cerebrovascular	1
		Borderline	1	Pplus	1
Possible drug-induced parkinsonism	4	Normal	1	Drug-induced parkinsonism	1
		PD	3	PD	1
				Pplus	2
Possible dystonia	6	Normal	5	Dystonia	5
		Borderline	1	Uncertain, cerebrovascular?	1
Possible ET	4	Normal	3	ET	3
		Borderline	1	ET	1

The borderline cases were re-evaluated by a specialist in nuclear medicine (L.F.) blinded to the clinical diagnosis at the time of evaluation. The most likely scan diagnosis was noted in each case. Two borderline scans were evaluated as normal, and three as PD. These cases were found in the six groups as follows: PD: none; possible PD: two borderline scans, both most likely normal; possible parkinsonism plus: one borderline scan, most likely PD (but still an uncertain diagnosis); possible drug-induced parkinsonism: none; possible dystonia: one borderline scan, most likely PD; possible ET: one borderline scan, most likely PD

PD, Parkinson's disease; Pplus, parkinsonism plus; ET, essential tremor

Most of the patients had been seen regularly in our out-patient clinic, and at the time of the retrospective evaluation, the mean duration of observation since the SPET scan was 14 months. In 22 patients, or 24%, the evaluation period was terminated prior to the time of evaluation because of death (ten patients) or referral to other departments or a general practitioner. The mean duration of observation differed in the three groups: For patients with a scan diagnosis of PD it was 19 months, for patients with a normal scan it was 16 months and in the group with borderline changes it was 8 months.

A direct impact of the [^{123}I]-β-CIT SPET investigations on management or treatment was found in the clinical notes for 25 of the patients. Twenty-four of these patients had been referred with a diagnosis of either possible PD or possible parkinsonism plus (Table 5). In 62% the result of the scan confirmed the clinical diagnosis.

Table 5. Impact of the result of the SPET investigation on management or diagnosis, in relation to the referral diagnosis

Diagnosis at the time of referral	No. of patients	Impact of scan result on management or diagnosis
Probable PD	16	0
Possible PD	41	20
Possible parkinsonism plus	19	4
Possible drug-induced parkinsonism	4	1
Possible dystonia	6	0
Probable essential tremor	4	0
Total	90	25

Discussion

Implications of results

This study was performed in a large group of patients consecutively referred for [^{123}I]-β-CIT SPET scans from a large movement disorder clinic. It reflects 2^1/$_2$ years' use of DAT receptor imaging by specialists in neurology. Previously only findings in smaller patient groups have been reported. Most of the referred patients had a tentative diagnosis of PD or parkinsonism plus.

In general the investigations were performed because the diagnosis was uncertain. The results of the SPET investigations correlated well with the clinical diagnoses at the time of evaluation. In 15 of the patients with a referral diagnosis of possible parkinsonism plus, DAT receptor imaging showed reduced tracer uptake. At the time of evaluation only one of these patients had a diagnosis other than PD or parkinsonism plus, i.e. vascular parkinsonism. In the group of 41 patients referred with possible PD, DAT receptor imaging showed reduced tracer uptake in 26. At the time of evaluation only two of these 26 patients had diagnoses other than PD or parkinsonism plus, i.e. vascular parkinsonism and dementia.

Theoretically, DAT receptor imaging should be able to differentiate vascular parkinsonism from the extrapyramidal syndromes. One study using technetium-99m TRODAT has suggested that this is the case [21]. The clinical criteria for vascular parkinsonism are not well established [22]. Atherosclerotic parkinsonism was first described in 1929, but consensus regarding this diagnosis as a clinical entity has not been reached. One of the reasons for this may be that vascular structural lesions in both the basal ganglia and the frontal cortex can be found in this syndrome. Pathological confirmation of this clinical entity is lacking [3]. Vascular lesions are also more frequent in PD than in controls. The reason for the variable results of DAT receptor imaging in patients with vascular parkinsonism may be that this clinical entity is heterogeneous.

In the group of 41 patients with possible PD, only 13 had a previous good response to dopaminergic medication. In some cases the investigation was used as a diagnostic probe before deciding whether the patient should begin treatment or not. Traditionally a trial of levodopa has been used as a diagnostic probe. In younger patients, however, use of a levodopa trial has been questioned, as it has been reported that even small doses of levodopa can prompt complications in PD at an early stage in the disease.

This retrospective study provides information on the tentative diagnoses before SPET investigation and the clinician's reaction to the scan, as well as the tentative diagnoses at an arbitrary time point after the investigations. The somewhat heterogeneous population very much resembles that examined by a neurological specialist during his or her daily clinical work. We found the SPET investigation to be clinically useful, and it caused a change in treatment, management or diagnosis in 27% of the patients. Among those patients with a referral diagnosis of possible PD or possible parkinsonism plus, an impact was found in 40% of cases (Table 5).

Methodological considerations

The diagnoses in this study were all clinical. We had only one autopsy-confirmed case. A recent study has proposed a high precision of clinical diagnosis by specialists in PD, with re-evaluation of an initial diagnosis of PD being necessary in only 8.1% of cases after a mean evaluation period of 6 years [23]. However, in that study the diagnosis was assessed neuropathologically at autopsy in only 13 of 800 patients. In five of these cases such assessment did not confirm PD, and only four patients (31%) had uncomplicated PD; hence the autopsy data suggest a much higher misdiagnosis rate [24].

In some of our patients, additional investigations may have increased the likelihood of accurate diagnosis at the time of evaluation. A follow-up investigation on a random group of patients would be a way to control the diagnoses, but definite diagnosis will still require neuropathological confirmation.

A high sensitivity and specificity were found for [^{123}I]-β-CIT SPET in this study,. This is in accordance with the findings of Booij et al. [16]. Comparable results could be expected, since the different cocaine analogues used – [^{123}I]-β-CIT and [^{123}I]-FP-CIT – have been found to produce similar results regarding discrimination of PD and correlation with age and severity of symptoms [25].

The borderline changes should possibly have been considered not to be parkinsonian. Patients with an extrapyramidal syndrome exhibiting parkinsonian symptoms would be expected to have a significant reduced striatal uptake of [^{123}I]-β-CIT reflecting the loss of at least about 50% of DAT receptors preceding neurological symptoms [13, 26]. Neuropathological data, F-DOPA positron emission tomography imaging [27] and clinical reports of early changes in, for instance, smelling [8] corroborate this. It is, however, possible that the early changes in the brain in parkinsonism plus are reflected in loss of DAT receptors to a lesser degree than is true in PD, in that the parkinsonism plus syndromes are characterised by significant post-synaptic changes early in the course of the disease.

Conclusion

This study has shown that DAT receptor imaging is a clinically useful investigation. The result of [^{123}I]-β-CIT SPET frequently caused a change in treatment, management or diagnosis, especially in patients with a tentative referral diagnosis of possible PD or parkinsonism plus.

Furthermore a high correlation was found between the scan diagnoses and the clinical diagnoses after a mean observation time of 14 months. [^{123}I]-β-CIT SPET was found to have a sensitivity of 97% and a specificity of 83%, suggesting a high positive predictive value of the investigation. This study supports the use of DAT receptor imaging as a diagnostic tool in PD and parkinsonism plus.

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