Original article

Early-stage [^{123}I]β-CIT SPECT and long-term clinical follow-up in patients with an initial diagnosis of Parkinson's disease

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Abstract. *Purpose:* Previous studies using dopamine transporter single-photon emission computed tomography (SPECT) to try and distinguish between patients with idiopathic Parkinson's disease (IPD) and patients with atypical parkinsonian syndromes (APS) have mainly focussed on patients with an already established clinical diagnosis of several years' duration. Differences in the pattern of striatal involvement between IPD and APS have been found in only few studies. We hypothesized that distinguishing SPECT features might be most pronounced at an early disease stage, and the purpose of the present study was to investigate this hypothesis.
Methods: The study included 72 patients with an initial clinical diagnosis of IPD, supported by decreased striatal [^{123}I]β-CIT binding on baseline SPECT. In ten patients, the diagnosis was changed to APS over a mean follow-up period of 62 months. We retrospectively compared the patterns of striatal involvement on the baseline SPECT scans between the group of patients (re)diagnosed with APS and the remaining 62 patients in whom a diagnosis of IPD was maintained.
Results: In the group of patients with APS, baseline [^{123}I]β-CIT binding in both caudate nuclei was lower than in the group of patients with IPD. In addition, putamen to caudate binding ratios were higher in the group of APS patients. In spite of these differences, individual binding values showed considerable overlap between the groups.
Conclusion: [^{123}I]β-CIT SPECT scanning in early-stage, untreated parkinsonian patients revealed a relative sparing of the caudate nucleus in patients with IPD as compared to patients later (re)diagnosed with APS. Nevertheless, the pattern of striatal involvement appears to have little predictive value for a later re-diagnosis of APS in individual cases.

Keywords: Parkinson's disease – Multiple system atrophy – Dopamine transporter – SPECT – Parkinsonian disorders

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Introduction

Two large clinicopathological studies in the early 1990s showed the accuracy of the clinical diagnosis of idiopathic Parkinson's disease (IPD) to be below 80% [1, 2]. A more recent study using current clinical criteria in 100 patients diagnosed with IPD showed a diagnostic accuracy of 90% [3]. In a specialist movement disorder service, the accuracy of the *final* clinical diagnosis of IPD even exceeded 98% [4]. Early in the course of the disease, when differentiating clinical features may not yet have developed, diagnostic accuracy is probably much lower. In the aforementioned study from a specialized movement disorders service, the *initial* clinical diagnosis was changed to one of the so-called atypical parkinsonian syndromes (APS) in more than one-quarter of the patients [4]. This "contamination" of the early-stage IPD population with patients suffering from APS could lead to a share of potential non-responders in fuure studies investigating the effects of neuroprotective agents. Improving the accuracy of the initial clinical diagnosis of IPD is not only of importance to future studies of neuroprotective agents, but would also enable us to provide more reliable information to patients and caregivers with respect to prognosis and expected response to symptomatic treatment.

In vivo imaging of striatal dopamine transporter (DAT) binding by means of single-photon emission computed tomography (SPECT) is a quantitative biomarker for IPD

onset, severity and progression [5–10]. Previous studies in which this technique was used to study differences in the pattern of degeneration of the nigrostriatal system between IPD and APS have so far shown inconsistent results. In some, a relative sparing of the caudate nucleus or a higher degree of asymmetry in striatal involvement distinguished between IPD and either multiple system atrophy (MSA) [11] or progressive supranuclear palsy (PSP) [12, 13] at a group level. In other studies, no differences whatsoever were found in striatal DAT binding between IPD and APS [14–16]. The inconsistency in these findings might be explained by the design of previous studies, in which subjects were generally included at advanced stages of disease. Considering the supposedly slower progression of dopaminergic hypofunction in the (posterior) putamen as compared with the caudate nucleus in the early phases of IPD [17], differences in caudate involvement between IPD and APS might very well become less pronounced with advancing disease stage. Along the same line of reasoning, faster progression of dopaminergic hypofunction in the putamen ipsilateral to the clinically most affected body half [17] can be expected to reduce the asymmetry of putaminal involvement with disease progression. It is therefore quite likely that differences in the pattern of dopaminergic hypofunction between IPD and APS will be most pronounced in the early stages of disease. Early-stage DAT SPECT imaging may thus be more sensitive in detecting such changes than DAT SPECT at later disease stages.

To date, few studies have been conducted to investigate the effects of treatment with dopaminergic agents on DAT SPECT binding in IPD patients [18, 19]. Although a (major) influence of anti-parkinsonian medication on DAT binding appears to be unlikely, this has not been proven conclusively. In particular, an influence of dopamine agonists on DAT binding cannot be excluded at present [19]. Most patients included in previous studies comparing DAT binding between IPD and APS patients were already using dopaminergic agents. Ideally, the potential value of DAT SPECT imaging in the differential diagnosis of parkinsonism should be assessed before pharmacological treatment is initiated.

The aim of the present study was to retrospectively compare the patterns of striatal involvement, visualized at baseline using [^{123}I]β-CIT SPECT scanning in early-stage, untreated patients with a clinical diagnosis of IPD, between those subjects in whom the initial diagnosis of IPD was changed to APS during a mean follow-up period of 62 months and those subjects in whom the initial diagnosis of IPD was maintained. In all patients included in the study, the initial clinical diagnosis of IPD was supported by a reduction of striatal [^{123}I]β-CIT binding on the baseline SPECT scan.

The experiments complied with the current laws in The Netherlands, inclusive of ethics approval.

Materials and methods

Subjects

A total of 77 patients with early-stage, untreated IPD diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDSBB) clinical diagnostic criteria [20] and reduced [^{123}I]β-CIT SPECT binding (see data processing section for details regarding criterion) at the time of the initial clinical diagnosis were recruited from the outpatient clinic for movement disorders at the VU University Medical Center (VUMC). In all patients, [^{123}I]β-CIT SPECT imaging was performed before the initiation of dopaminomimetic therapy. None of the subjects was using a compound that potentially interferes with [^{123}I]β-CIT SPECT binding (i.e. amphetamine, cocaine or bupropion). All subjects gave written informed consent to the research protocol, which was approved by the local medical ethical committee of the VUMC. Ethics review criteria conformed to the Helsinki Declaration. Of the total group of 77 patients, four were lost to follow-up and one had an uncertain diagnosis, leaving a group of 72 patients for further analysis. Disease duration was calculated on the basis of the patients' subjective estimate of the time of occurrence of the first motor symptoms. Side of onset was based on the body half in which the first clinical (motor) symptoms occurred. Unified Parkinson's Disease Rating Scale motor scores (UPDRS III [21]) were obtained by a trained neurologist.

SPECT imaging

SPECT imaging was performed using a system dedicated to brain topography, the SME 810X system (Strichman Medical Equipment Inc., Medfield, MA, USA). The Strichman camera consists of 12 individual crystals each equipped with a focussing collimator. The transaxial resolution of this camera is 7.6 mm full-width at half-maximum (FWHM) of a line source in air. Subjects received potassium iodide orally in order to block thyroid uptake of free radioactive iodine. [^{123}I]β-CIT (Amersham Cygne, Eindhoven, The Netherlands; specific activity >185 MBq/nmol; radiochemical purity >99%) was injected intravenously at an approximate dose of 110 mBq. ^{123}I labelling, acquisition, attenuation correction and reconstruction of images were performed as described previously [22]. Image acquisition was performed 24 h post injection. The measured concentration of radioactivity was expressed in Strichman Medical Units (SMUs; 1 SMU=100 Bq/ml as specified by the manufacturer).

Clinical follow-up

Clinical follow-up was performed by examining patient charts 36–80 months (mean ± SD, 62±11 months) after [^{123}I]β-CIT SPECT imaging. Whenever necessary, supplementary data were obtained during the next scheduled appointment at the outpatient clinic. Diagnostic criteria used in the re-evaluation of the clinical diagnosis were the UK-PDSBB clinical diagnostic criteria for IPD [20], the AAS/AAN criteria for MSA [23], the NINDS-SPSP criteria for PSP [24] and the consensus criteria for dementia with Lewy bodies (DLB) [25]. In several patients, data from magnetic resonance imaging (MRI, n=11) and/or the results of [^{123}I]iodobenzamide (IBZM) SPECT scans (n=12) were available. Vascular lesions in the striatum on so-called fast-FLAIR and/or T2-weighted MRI were considered supportive of vascular parkinsonism. A hypointense putamen with a hyperintensive rim and/or hyperintensities in the brainstem on fast-FLAIR and/or T2-weighted MRI were considered supportive of MSA. Reduced D_2 binding on IBZM SPECT images was considered supportive of either MSA or PSP. Re-evaluation of

the 72 patients with an initial diagnosis of IPD yielded 62 cases of IPD. In ten patients, the diagnosis of IPD was changed to APS; these were seven cases of MSA, two cases of DLB and one case of PSP. Thus, at least 13% of our original study population of 77 patients were re-diagnosed with APS during the follow-up period. Subject characteristics at baseline are listed for each group in Table 1.

Data processing

For the analysis of striatal [^{123}I]β-CIT binding, two consecutive transverse slices representing the most intense striatal binding were analysed. A standard anatomical region of interest (ROI) template (constructed according to a stereotactic atlas and including regions for caudate nucleus, putamen and occipital cortex) was placed bilaterally on the images (Fig. 1). Small variations of individual brains required movement of the fixed ROIs, without changing their size and shape, within the template for optimal fitting. Estimates of specific striatal binding were made by subtracting occipital counts (non-specific binding; mean of the two slices) from striatal counts. Specific to non-specific [^{123}I]β-CIT binding ratios were then calculated for left and right putamen and left and right caudate nucleus. In addition, bilateral putamen to caudate ratios and asymmetry indices for the putamen and caudate nucleus were computed, using the following formulas: putamen binding ratio/caudate binding ratio and |(right binding ratio − left binding ratio)/(right binding ratio + left binding ratio)|, respectively. Subsequently, all ratios were recoded into the most symptomatic (contralateral) side and least symptomatic (ipsilateral) side, based on the side of onset of the first parkinsonian symptoms. [^{123}I]β-CIT binding was considered abnormal, i.e. to reflect degeneration of nigrostriatal dopaminergic neurons, when the binding ratios of either right or left caudate or right or left putamen were reduced to more than two SD values from the mean of healthy controls (control data from our laboratory [26], n=10, age 44.7±16.9 years, binding ratio left caudate 6.9±1.6, right caudate 6.9±1.5, left putamen 6.1±2.0, right putamen 6.0±1.6 (mean ± SD)).

Statistical analysis

Group differences between IPD and APS groups in the distribution of gender, side of onset and modified Hoehn and Yahr [27] scores were analysed by means of chi-square tests. All analyses with regard to group differences in age, disease duration, follow-up period and UPDRS motor scores [21], as well as all analyses with regard to the dependent variables, i.e. the [^{123}I]β-CIT SPECT binding ratios and asymmetry indices, were analysed by univariate analysis of variance. Estimates of effect size are reported using eta squared (η^2), which represents the proportion of the total variability in the dependent variable (i.e. SPECT parameter) that is accounted for by the independent variable (IPD or APS group membership). Two of the dependent variables met with the assumption of normality, which is required for univariate analysis of variance, only after transformation by means of a natural logarithm (i.e. ipsilateral and contralateral caudate binding ratio). Correlation analysis between clinical parameters and [^{123}I]β-CIT SPECT ratios was performed by means of Pearson bivariate correlation. All analyses were performed at a significance level of 0.05 (two-tailed). Analysis was done using the SPSS 11.0 software package (SPSS Inc., Chicago, USA).

Table 1. Subject characteristics at baseline

Characteristics	IPD[a] (n=62)	APS[a] (n=10)
Sex (male/female)	39/23	5/5
Age (years, mean ± SD)	60.0±13.3	55.9±9.1
Disease duration (years, mean ± SD)	2.7±2.0	1.7±0.9
Follow-up period (months, mean ± SD)	62±11	61±10
Side of onset (right/left)	33/29	7/3
Modified HY score (1/1.5/2/2.5)	20/3/18/21	2/0/2/6
UPDRS motor score (mean ± SD)	18.4±7.0	22.1±6.0

IPD idiopathic Parkinson's disease, *APS* atypical parkinsonian syndromes, *HY* Hoehn and Yahr, *UPDRS* Unified Parkinson's Disease Rating Scale

[a]Clinical diagnosis at follow-up. All other data were measured at baseline

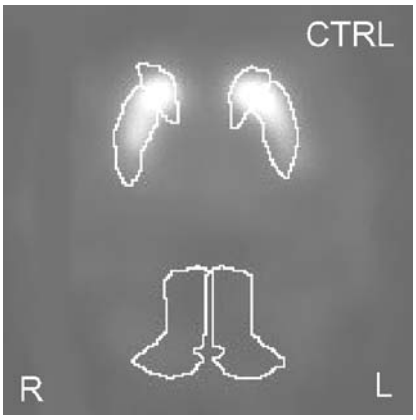

Fig. 1. [^{123}I]β-CIT SPECT image of a healthy volunteer. A standard anatomical ROI template (constructed according to a stereotactic atlas and including regions for caudate nucleus, putamen and occipital cortex) has been placed bilaterally. Transverse slice from the brain at the level of the striatum (approximately 3 cm above the orbitomeatal line). Levels of SPECT activity are coded from low (*black*) to high (*white*) and have been scaled to the maximum pixel value in the image

Results

Analysis of confounding factors

Patients with IPD and APS did not differ with regard to age, sex distribution, follow-up period, distribution of side of onset, disease duration, distribution of modified Hoehn and Yahr [27] scores or UPDRS motor scores [21].

Analysis of [^{123}I]β-CIT binding in IPD and APS

Group averages of specific to non-specific [^{123}I]β-CIT SPECT binding ratios, putamen to caudate ratios and asymmetry indices are listed in Table 2. No significant differences were found with respect to the [^{123}I]β-CIT binding ratios in the putamen. Ligand binding was, however, lower in both ipsilateral (F[1, 71]=9.97; p=0.002; η^2=0.125, Fig. 2) and contralateral (F[1, 71]=5.62; p=0.020; η^2=0.074, not illustrated) caudate nucleus of the

Table 2. Specific to non-specific [^{123}I]β-CIT SPECT binding ratios, putamen to caudate ratios and asymmetry indices

	Putamen binding		Caudate binding		P/C		AI	
	Contra	Ipsi	Contra*	Ipsi*	Contra*	Ipsi**	Putamen	Caudate
IPD (*n*=62)	1.7±0.5	2.3±0.7	3.6±1.1	4.2±1.2	0.48±0.09	0.56±0.11	0.17±0.91	0.09±0.05
APS (*n*=10)	1.6±0.8	2.0±1.0	2.9±1.1	3.3±1.4	0.57±0.15	0.62±0.14	0.15±0.12	0.06±0.04

Data are shown as mean ± SD

P/C putamen to caudate ratio, *AI* asymmetry indices, *Contra* contralateral to side of onset of first clinical (motor) symptoms, *Ipsi* ipsilateral to side of onset of first clinical (motor) symptoms, *IPD* idiopathic Parkinson's disease, *APS* atypical parkinsonian syndromes

*Significantly different between IPD and APS (p0.05)

**Trend towards difference between IPD and APS (p0.1)

group of patients with APS relative to the group of patients with IPD. Furthermore, the putamen to caudate ratio in the contralateral striatum was higher in the group of patients with APS relative to the group of patients with IPD (F[1, 71]=7.20; p=0.009; η^2=0.093, Fig. 3). There was a trend towards a higher putamen to caudate ratio in the ipsilateral striatum (F[1, 71]=2.97; p=0.089; η^2=0.041, not illustrated). In spite of these differences at group level,

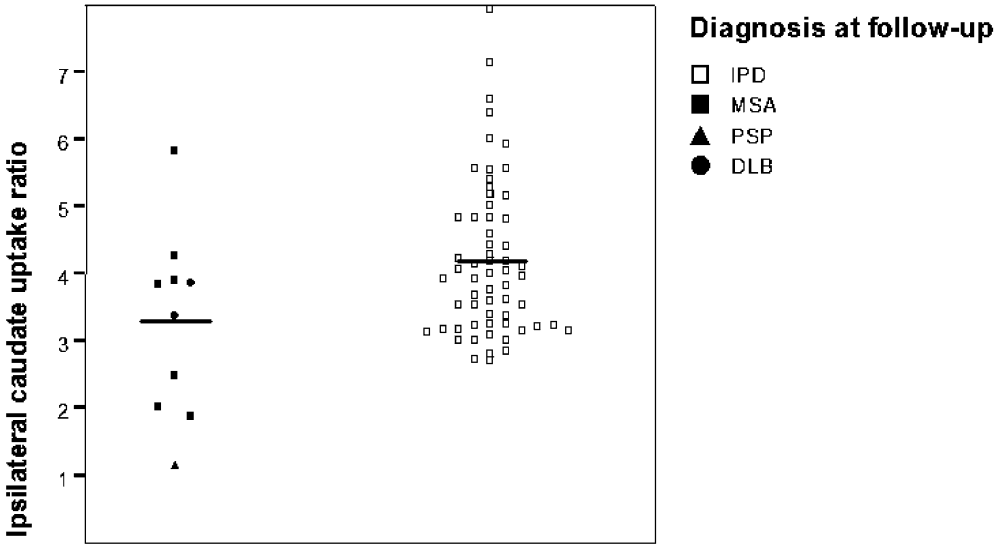

Fig. 2. Scatterplot of specific to non-specific [^{123}I]β-CIT SPECT binding ratios in the caudate nucleus ipsilateral to the side of onset of first clinical (motor) symptoms. Solid lines indicate the mean binding ratios

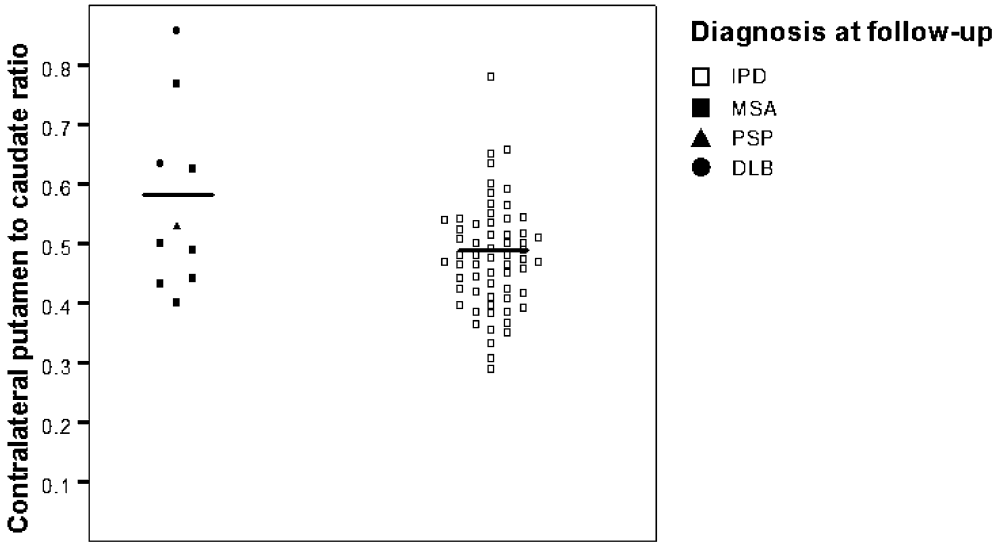

Fig. 3. Scatterplot of putamen to caudate ratios contralateral to side of onset of first clinical (motor) symptoms. Solid lines indicate the mean ratios

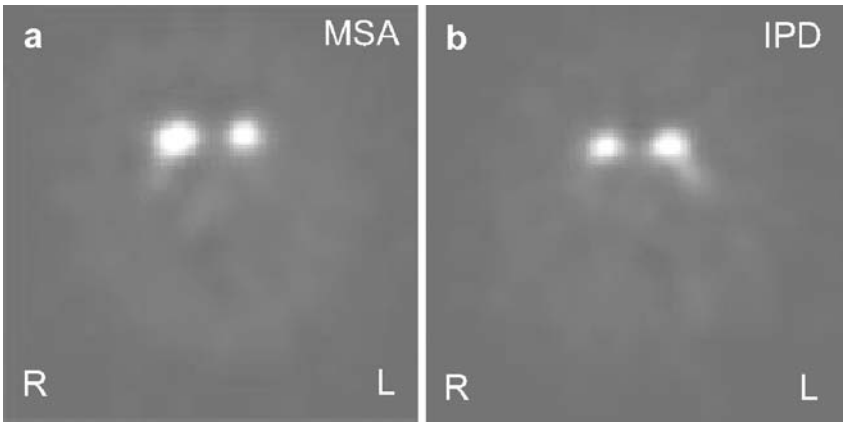

Fig. 4. Baseline [^{123}I]β-CIT SPECT images of two patients with a parkinsonian syndrome. Transverse slices from the brain at the level of the striatum (approximately 3 cm above the orbitomeatal line). Levels of SPECT activity are coded from low (*black*) to high (*white*) and have been scaled to the maximum pixel value in each individual image. **a** Patient suffering from MSA, with relatively spared caudate binding and significantly reduced putamen binding. **b** IPD patient with relatively spared caudate binding and significantly reduced putamen binding. Note the similarity in the patterns of striatal involvement in images **a** and **b**, a phenomenon which is also reflected in the overlapping distributions in both Fig. 2 and Fig. 3

individual patients with APS and IPD could have quite similar patterns of striatal involvement (Fig. 4). No differences were found in asymmetry indices.

Correlation of striatal [^{123}I]β-CIT binding with clinical parameters in IPD and APS

In patients with IPD, correlation analysis revealed a significant negative correlation between disease duration and both contralateral (r=−0.30, p=0.020) and ipsilateral (r=−0.36, p=0.004) striatal [^{123}I]β-CIT binding. In the IPD group, significant correlations were also found between [^{123}I]β-CIT binding and disease stage and severity. Contralateral striatal [^{123}I]β-CIT binding was negatively correlated with UPDRS motor score (r=−0.34, p=0.006) and there was a trend towards a negative correlation with Hoehn and Yahr stage (r=−0.24, p=0.061). Ipsilateral striatal [^{123}I]β-CIT binding was negatively correlated with both UPDRS motor score (r=−0.48, p=0.000) and Hoehn and Yahr stage (r=−0.40, p=0.001). In patients suffering from APS, no correlations could be found between striatal [^{123}I]β-CIT binding and either disease duration or stage or severity.

Discussion

The results of this study demonstrate that within a cohort of individuals with an initial clinical diagnosis of IPD, supported by a loss of striatal [^{123}I]β-CIT binding as evidenced by baseline SPECT imaging, the degree of caudate involvement differed between a group of patients later (re)diagnosed with APS and a group of patients in whom the diagnosis of IPD was maintained. Caudate [^{123}I]β-CIT binding was reduced more in those patients later to develop APS than in patients with IPD. This was reflected both in caudate [^{123}I]β-CIT binding ratios and in putamen to caudate ratios.

A higher degree of caudate involvement in APS relative to IPD was previously reported by Varrone et al. for MSA in a study using [^{123}I]β-CIT SPECT [11], and by Antonini et al. [12] and Messa et al. [13] for PSP using [^{123}I]FP-CIT and [^{123}I]β-CIT SPECT, respectively. By contrast, others were unable to find any differences in caudate involvement between IPD and either PSP or MSA [14–16]. This discrepancy may be related to the fact that in the latter studies IPD patients were included at more advanced stages of disease, when caudate sparing in IPD is likely to be less pronounced. In the present study, we did not observe differences in putaminal involvement between APS and IPD. This is in line with most previous studies [12–16], an exception being the aforementioned study by Varrone et al. [11], in which the putamen ipsilateral to the most affected body half was more severely affected in MSA.

The relative sparing of the caudate nucleus in IPD observed in the present and some previous imaging studies is in line with the results of post-mortem studies that have revealed a more severe degeneration of dopaminergic fibres projecting from the ventrolateral tier of the substantia nigra to the putamen and a relative sparing of projections to the caudate nucleus in IPD [28, 29]. By contrast, in PSP, post-mortem studies have shown a diffuse loss of nigrostriatal projections, resulting in a uniform dopamine depletion throughout the striatum [30, 31]. In MSA, patterns of degeneration are heterogeneous, with diffuse involvement of the substantia nigra in some and a pattern analogous to IPD in others [32].

Varrone et al. reported a less marked asymmetry in the loss of DAT binding from the putamen in MSA relative to IPD [11], a result that could not be replicated in the current or any of the other previous studies. As far as the present study is concerned, the absence of a difference in asymmetry indices between the IPD and APS groups

could possibly be related to the fact that all patients enrolled in the present study had an initial diagnosis of IPD, thus leading to a potential overrepresentation of APS patients with an asymmetrical presentation.

In line with previous studies [5, 8–10, 33], we found strong correlations between clinical parameters and striatal [^{123}I]β-CIT binding in IPD patients. No correlations between clinical parameters and [^{123}I]β-CIT binding were found in APS patients. An obvious explanation is the relatively small APS group size (n=10), a notion supported by several fairly high Pearson correlation coefficients (up to −0.46). Moreover, motor performance in APS patients is at least partly caused by degeneration of post-synaptic striatal neurons and may also be influenced by non-dopaminergic (e.g. cerebellar) mechanisms.

In the present study, the initial diagnosis of IPD was changed in 13% of cases after a mean clinical follow-up period of 62 months. In a recent study by Hughes et al. [4], more than one-quarter of patients with an initial clinical diagnosis of IPD later appeared to be suffering from an APS. The most likely explanation for the higher initial diagnostic accuracy in the present study is the use of baseline DAT SPECT imaging to support the clinical diagnosis, thus at least excluding several other causes of parkinsonism. Another important difference between the study by Hughes et al. and ours is that in the former study pathological confirmation of the clinical diagnosis was available. In spite of a mean disease duration at clinical follow-up of as much as 92 months in the present study, we therefore cannot exclude the possibility that some subjects in our study in whom a clinical diagnosis of IPD was so far maintained may yet turn out to be suffering from an APS.

Considering the extensive overlap among the values of individual [^{123}I]β-CIT binding ratios of patients with IPD and of patients with APS and the similarities of individual SPECT images of IPD and APS patients, the value of early-stage DAT SPECT imaging for a later re-diagnosis of APS in individual cases would appear to be limited. Quite possibly, however, differentiation between the various parkinsonian syndromes at the individual level may be improved by further methodological refinements and/or use of a combination of imaging techniques. For example, there is some preliminary evidence from a recent DAT binding study using positron emission tomography with [^{11}C]-WIN 35,428 as a ligand that a technique with higher spatial resolution serves better to distinguish IPD patients from patients with APS [34]. Alternatively, DAT SPECT could be combined with SPECT imaging of post-synaptic striatal elements, such as dopamine D_2 receptor imaging using [^{123}I]IBZM or [^{123}I]iodobenzofuran as ligands [16], although intact binding to the dopamine D_2 receptor does not seem to exclude incipient MSA or PSP [35].

In conclusion, early-stage [^{123}I]β-CIT SPECT scanning in untreated patients with an initial clinical diagnosis of IPD demonstrated a relative sparing of the caudate nucleus in the group of individuals in whom a diagnosis of IPD was maintained over an extended follow-up period relative to the group of individuals later re-diagnosed with an APS. In spite of this difference at a group level, the predictive value of early-stage [^{123}I]β-CIT SPECT imaging for a later re-diagnosis of APS in individual cases remains limited. Further methodological and/or technical improvements may yet provide us with a biological marker that also proves useful at the level of the individual patient.

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