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Diagnostic Value of ^{123}I-Ioflupane and ^{123}I-Iodobenzamide SPECT Scans in 248 Patients with Parkinsonian Syndromes

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Key Words
Parkinsonism · Idiopathic Parkinson's disease · Single Photon Emission Computed Tomography · ^{123}I-ioflupane · ^{123}I-iodobenzamide

Abstract
Background: SPECT is one of the most employed techniques in the diagnostic workup of idiopathic Parkinson's disease (IPD). Despite its widespread use, the exact diagnostic accuracy of this technique in parkinsonian syndromes remains controversial. ***Methods:*** In this study, we investigated the diagnostic accuracy of an initial ^{123}I-ioflupane (FP-CIT) and/or ^{123}I-iodobenzamide (IBZM) SPECT to differentiate between IPD and other parkinsonian disorders. 248 patients underwent a SPECT scan because of an as yet unclassified parkinsonian syndrome in our clinic between 2001 and 2006. Gold standard was the clinical diagnosis derived from the latest available clinical record, or, when this was not possible, a new complete physical and neurological examination by a blinded movement disorder specialist neurologist. Mean follow-up between SPECT and the latest clinical information was 18 months (range 3 months to 5 years). ***Results:*** 223 of the 248 patients were clinically definitely diagnosed after follow-up: IPD 127, atypical parkinsonian syndromes (APS) 27, essential tremor (ET) 22, vascular parkinsonism (VP) 16, drug-induced parkinsonism (DIP) 5, doubt between PD and APS 2, other diseases without dopaminergic involvement 24. The mean odds ratio (95% CI) for FP-CIT SPECT's ability to distinguish between IPD and ET was 82 (11–674); between IPD and VP 61 (8–490); between IPD and DIP 36 (2–697) and between IPD and APS was 1 (0–4). The odds ratio for the IBZM SPECT tracer to differentiate between IPD and APS was 7 (2–17). ***Conclusions:*** FP-CIT SPECT is accurate to differentiate patients with IPD from those with ET, and IPD from VP and DIP. The accuracy of both FP-CIT and IBZM SPECT scans to differentiate between IPD and APS is low.

Introduction

Idiopathic Parkinson's disease (IPD) is the second most common neurodegenerative disorder with a prevalence in industrialized countries of 0.3% in the entire population and about 1% in people over 60 years of age

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[1]. The exact cause of IPD is still unknown, but the main pathological hallmark of the disease is the loss of dopaminergic neurons in the basal ganglia [2]. Diagnosis is based on clinical criteria [3]. In most cases, the diagnosis of IPD is straightforward when cardinal clinical signs and symptoms as bradykinesia, rigidity, resting tremor and postural instability are present [3]. However, solely on clinical grounds it is, especially in the early stages, often difficult to differentiate IPD from other parkinsonian syndromes. Diseases resembling IPD in an early stage are multiple system atrophy (MSA), progressive supranuclear paralysis (PSP), diffuse Lewy body disease (DLBD), but also vascular parkinsonism (VP), drug-induced parkinsonism (DIP) and essential tremor (ET) [4–9]. Since the prognosis and medical treatment are different in the various parkinsonian syndromes, an accurate and early diagnosis is essential for optimal counseling. SPECT is widely used to visualize the integrity of the nigrostriatal dopaminergic system. SPECT with various tracers labeling presynaptic dopamine transporters (such as ^{123}I-ioflupane – FP-CIT) has been shown to correlate with clinical severity and disease progression of IPD [10–14]. The uptake of these radiotracers, however, has also been shown to be decreased in the atypical parkinsonian syndromes (APS: i.e. MSA, PSP and DLBD) [15–18]. SPECT with tracers labeling postsynaptic dopamine receptors (such as ^{123}I-iodobenzamide – IBZM) have been used to differentiate IPD from APS [17, 19, 20]. Some have suggested even that the combination of presynaptic SPECT and postsynaptic SPECT scan gives better discrimination between IPD and APS [17, 21]. Despite their widespread use, the exact diagnostic accuracy of these techniques in parkinsonian syndromes remains controversial [22–24]. In the present study, we investigated the diagnostic accuracy in 248 patients in whom FP-CIT and/or IBZM SPECT scans were performed because of uncertainty on the diagnosis of their parkinsonian syndrome.

Patients and Methods

Subjects

We see an estimated 250 new patients (primary and secondary referrals and requests for second opinions) with parkinsonism in our neurology outpatient clinic each year, of which about 20% are referred for SPECT scintigraphy. Patients who did not undergo SPECT scanning were mainly patients presenting with a clear unequivocal diagnosis of their parkinsonism, and referrals who already had SPECT scintigraphy elsewhere.

From February 2001 to February 2006, 301 patients with parkinsonism were subjected to a SPECT scan in our hospital. Fifty-three patients were excluded because they already had a clear diagnosis and underwent SPECT as part of a diagnostic workup for a deep brain stimulation procedure, where one wants to exclude diagnoses other than IPD. The included 248 patients all suffered an as yet unclassified parkinsonian syndrome.

Depending on the clinical differential diagnosis of the neurologist, a FP-CIT (n = 80), an IBZM SPECT (n = 38) or both scans (n = 130) were performed.

The study was approved by the University Hospital Maastricht Institutional Review Board and all patients who were re-examined clinically to reach a definite diagnosis gave informed consent.

Fifty-nine percent of the 248 patients were male. The mean age was 65 years with a range from 21 to 96 years (standard deviation, SD, 11 years; see also table 1 for demographic and clinical parameters). The initial probable diagnosis of the neurologist before SPECT imaging was IPD in 125 patients, APS (MSA, PSP or DLBD) in 41 patients, VP in 9, ET in 10 and DIP in 2 patients. In 61 cases, the initial probable diagnosis was solely defined as parkinsonism.

The mean Hoehn and Yahr score was 2.4 (range 1–5; SD 1.2). Of all patients, 37% were on dopaminergic drugs before they were referred for SPECT scanning.

The mean duration of the complaints before SPECT imaging was 45 months (range 2–250; SD 45), and the clinical follow-up after the SPECT scan was at least 3 months with a mean (SD) of 18 (15) months. If a patient underwent both scans, the mean elapsed time between the FP-CIT and IBZM SPECT was 40 days (range 1–1,460; median 5; SD 178 days).

Acquisition of Clinical Data and Final Clinical Diagnosis

Two investigators (A.V., T.N.) checked each patient record and filled in a standard form. The investigators established a clinical diagnosis according to generally accepted clinical criteria [3, 8, 25–28]. If the investigators did not reach consensus, or if the patient did not fulfill the accepted criteria for a final diagnosis, a movement disorder specialist neurologist (A.W., W.W.) was asked for advice. In case of persistent discussion, the movement disorder specialist could decide to contact the referring neurologist, to phone the patient or to ask the patient to visit the clinic for re-examination by a movement disorder specialist neurologist (A.W., F.V., W.W.).

Single Photon Emission Computed Tomography

In this study, FP-CIT (General Electrics Health, Eindhoven, The Netherlands) was used to visualize the integrity of the presynaptic dopaminergic system and IBZM (General Electrics Health, Eindhoven, The Netherlands) to visualize the postsynaptic dopamine receptors. Medication which could interfere with the radiotracer was stopped at least 5 half-life times before the SPECT was made. SPECT scans were performed with a triple head camera (MultiSPECT3, Siemens, Ohio, USA) equipped with high-resolution collimators. A semi-automatic template model program was used to calculate the ratios between left striatal and right striatal and occipital regions, respectively. Total time of acquisition was 30 min (45 s per frame for 40 views per detector), zoom factor: 1.00 and matrix size: 128 × 128. Filtered back-projection acquisition was performed [29].

Images were filtered using a Butterworth filter with a cut-off value of 0.4–0.5 and an order of 5. The ratios were corrected using

Table 1. Demographic and clinical variables for each patient subgroup before SPECT scan

Final clinical diagnosis	Age, years	Females	Males	HY score[1]	Duration before SPECT months	Follow-up after SPECT months	Dead at the moment of data analyses
IPD (n = 127)	64 (56–72)	44	83	2 (1–3)	30 (12–60)	16 (8–36)	7
APS (n = 27)	67 (67–73)	14	13	3 (2–4)	23 (12–39)	13 (4–24)	8
IPD or APS (n = 2)	59 (40–75)	2	0	1.5 (1–2)	48 (36–60)	20 (12–28)	–
ET (n = 22)	68 (62–74)	11	11	2 (1–2)	48 (27–114)	20 (9–39)	2
VP (n = 16)	73 (66–78)	3	13	3 (2–4)	24 (12–42)	7 (4–29)	4
DIP (n = 5)	60 (58–68)	2	3	3 (2–4)	48 (19–72)	12 (4–33)	1
Other (n = 24)	65 (53–78)	13	11	3 (2.5–3)	36 (11–63)	7 (4–24)	2
Inconclusive (n = 25)	68 (57–77)	12	13	2 (2–4)	36 (13–72)	3 (1–20)	6
Total (n = 248)	67 (58–74)	100	148	2 (2–3)	36 (12–60)	13 (5–27)	30

HY = Hoehn and Yahr. Values for age, HY score, duration before and follow-up after SPECT are expressed as median (25–75 interquartile range).

[1] HY scores are formally restricted to IPD, but we have assessed these also in the other patient groups to facilitate comparison between these groups.

Alderson's brain phantom with known activities in the caudate nucleus and putamen. A binding of two SDs below or above healthy controls was considered as abnormal (FP-CIT 8.25, SD 1.85, for putamen; 7.76, SD 1.77, for caudate nucleus; IBZM 3.58, SD 0.18, for striatum). The scans were analyzed by a nuclear specialist blinded to the clinical diagnosis.

Data Analysis

Descriptives are presented as median and interquartile ranges, unless otherwise specified. To determine the accuracy to differentiate between IPD, ET and other parkinsonian syndromes sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic odds ratio (OR) with 95% confidence intervals (95% CI) were calculated. This was determined for the initial probable diagnosis of the neurologist, FP-CIT and IBZM SPECT results and the combination of both. Finally, we calculated the additional value of judging the caudate nucleus FP-CIT binding ratios in comparison with only putamen FP-CIT binding.

All descriptive analyses were made with software SPSS 11.0 for Windows (SPSS, Chicago, Ill., USA) and the accuracy parameters were determined with Stata/SE9.

Results

In 154 of the 248 cases, the investigators reached consensus and were certain enough to make a final diagnosis from the clinical records alone, according to generally accepted criteria [3, 8, 25–28]. Of the remaining 94 patients, 5 patients had died, 2 could not be traced and 2 lived outside the district.

In 27 of the 85 cases still without final diagnosis the referring neurologist was phoned, and in 5 cases the patient, to obtain information about the follow-up period. Finally, 53 patients were asked to visit our clinic for re-examination. 45 of these gave informed consent. Most important reasons for refusing consent for re-examination were decreased mobility, living in a nursing home and anxiety. Figure 1 presents a flowchart of patients included and excluded from the analysis.

In 223 of the 248 patients, the final clinical diagnosis after follow-up was known: IPD in 127 patients, APS in 27 (n = 17 MSA, n = 8 PSP, n = 2 DLBD), unclear but IPD or APS in 2, ET in 22, DIP in 5 and VP in 16 patients. Of the 16 patients diagnosed with VP, 6 underwent MRI scan and 10 underwent CT scan. In 10 of the 16 patients, vascular lesions were visible in typical places according to the criteria formulated by Zijlmans et al. [26]. All the other patients had suffered at least one stroke, but their vascular lesions on CT or MRI of the cerebrum were at nontypical places like capsula interna, parietal or occipital lobe. However, all patients had parkinsonism and a time relationship (acute or delayed) between stroke and parkinsonism or in case of multiple subcortical white matter lesions an insidious onset of parkinsonism and no exclusion criteria for VP.

Twenty-four patients were diagnosed with another diagnosis without dopaminergic involvement; i.e. there was no clear indication of parkinsonism (n = 8), psychogenic parkinsonism (n = 1), normal pressure hydrocephalus (n = 2), Alzheimer's disease (n = 4), autonomic failure

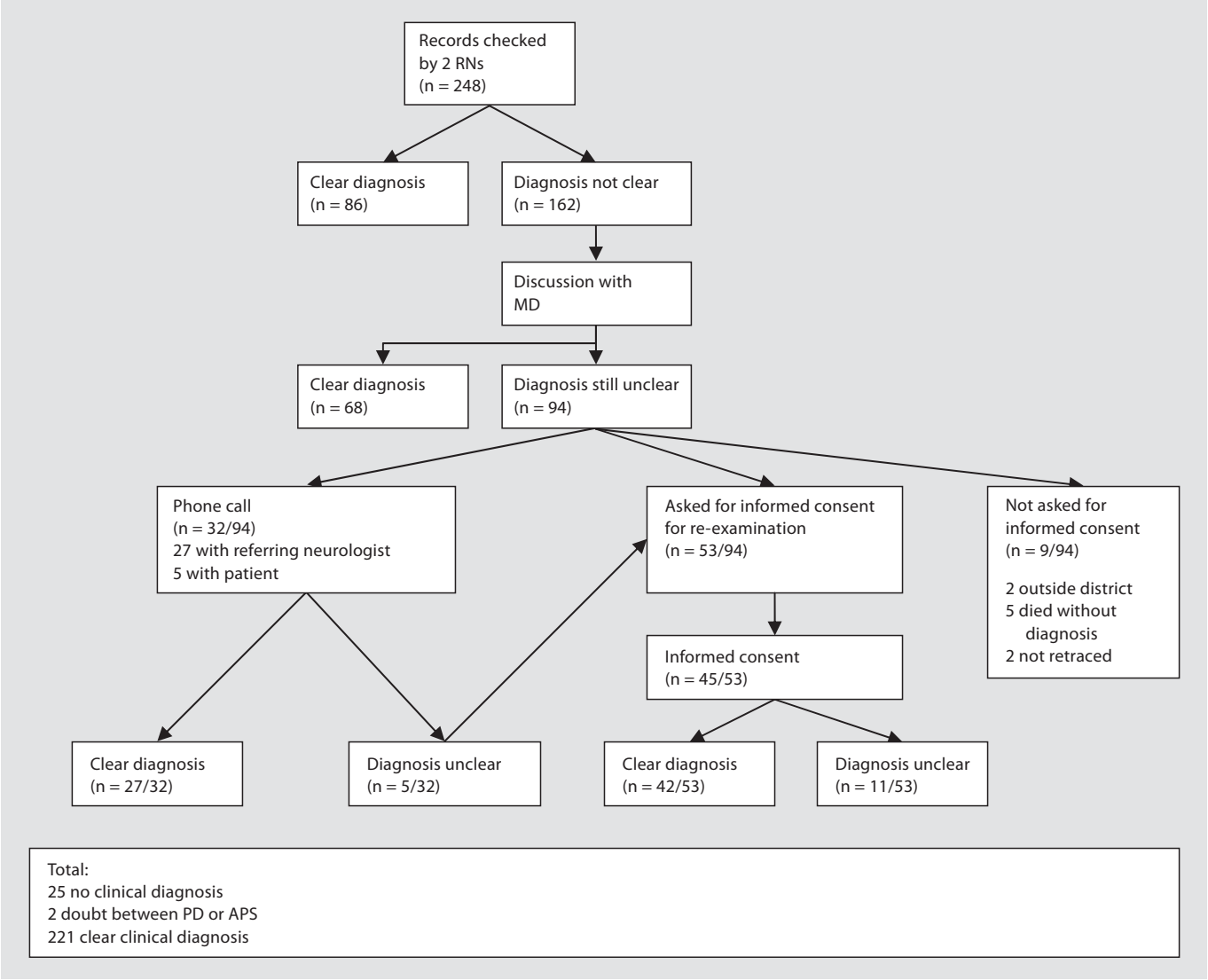


Fig. 1. Flowchart. RN = Resident in neurology; MD = movement disorder specialist.

(n = 1), corticobasal degeneration (n = 1), frontotemporal dementia (n = 1), alcohol abuse (n = 1), Meige syndrome (n = 1), Niemann-Pick syndrome (n = 1), familiar dominant tremor (n = 1), dystonia (n = 1), inconclusive but no dopaminergic involvement (n = 1).

The absolute tracer binding rates of FP-CIT and IBZM SPECT scans for each parkinsonian subgroup are shown in figure 2. From this figure, one sees that the median of the absolute putamen FP-tracer binding ratios in the IPD group as well as in the APS group is decreased compared with, for example, ET patients.

The striatal IBZM binding ratios in the APS group are decreased in comparison with the IPD group. However, discrimination between the groups is difficult, because of a large overlap in ranges.

Besides the diagnostic accuracy for the different subgroups of patients, we also determined the accuracy of SPECT and the initial probable diagnosis of the clinician for each individual patient separately. A summary of the results of presynaptic and postsynaptic SPECT scanning for all patients in the different subgroups of the final diagnoses (IPD, ET, VP and APS) is given in table 2.

From this table, the numbers of true positives, true negatives, false positives and false negatives are derived to calculate the sensitivity, specificity, PPV, NPV and mean OR for the differentiation between IPD versus ET,

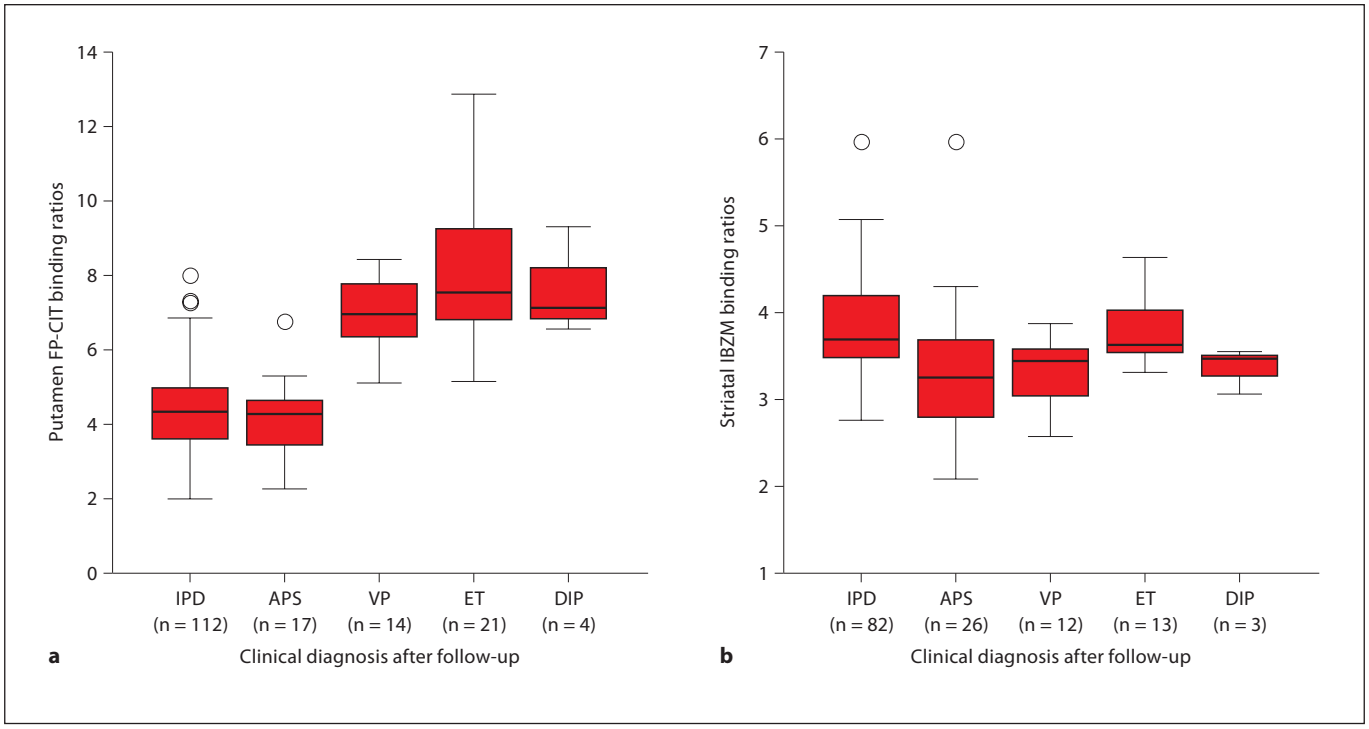


Fig. 2. a Box plot of the median FP-CIT binding ratios and interquartile ranges for each subgroup. **b** Box plot of the median IBZM binding ratios and interquartile ranges for each subgroup.

IPD versus VP, IPD versus DIP and IPD versus APS. An overview is given in table 3.

As shown in table 3, FP-CIT SPECT's ability to distinguish between patients with IPD and patients with ET is high. FP-CIT scans are also relatively accurate to differentiate patients with IPD from those with VP or DIP. In these 3 situations, sensitivity is 80% and specificity 95–100%. With a PPV above 95%, an abnormal FP-CIT SPECT scan is highly predictive of IPD. However, the NPV of a normal SPECT for ET, VP or DIP is low (15–48%). This is a consequence of the fact that not only 20 of the 21 ET patients and all 14 VP and 4 DIP patients had a normal FP-CIT SPECT scan, but also 22 of the 112 IPD patients.

The addition of IBZM SPECT only leads to a small (not statistically significant) increase in accuracy in the discrimination between patients with IPD from VP and patients with IPD from DIP (tables 2 and 3).

The differentiation between IPD and APS (PSP, MSA and DLBD) by both FP-CIT and IBZM SPECT scored relatively low accuracy. Specificity and NPV are low, as 62% of the APS patients and 20% of the IPD patients have lowered striatal IBZM tracer binding. The combination of FP-CIT and IBZM SPECT scored only minimally increased accuracy (table 3).

We expected APS patients to have a more diffusely decreased striatal FP-CIT binding rate in comparison to patients with IPD, showing mainly a selective loss of tracer binding in the putamen: we calculated the additional value of judging the FP-CIT uptake in the caudate nucleus in comparison with only the uptake in the putamen. The FP-CIT binding of the caudate nucleus was decreased (>2 SD below the mean of the healthy controls) in 14 of the 127 IPD patients, 1 of the 15 MSA patients and in 2 of the 9 PSP patients and in none of the 3 patients with DLBD. All patients with low caudate FP-CIT binding ratios also had decreased putamen FP-CIT binding. So with an OR (95% CI) of 1 (0.3–4) judging of the FP-CIT tracer binding in the caudate nucleus does not lead to an increase in accuracy to differentiate between IPD and APS.

In the present study, differentiation among the different APS (MSA, PSP and DLBD) was not accurate with FP-CIT SPECT: 7 of the 9 MSA patients, as well as 4 of the 6 PSP patients and 2 of the 3 DLBD patients had abnormal FP-CIT SPECT scan results. IBZM SPECT could not discriminate between patients with MSA and PSP:

Table 2. SPECT results for each patient subgroup

Clinical diagnosis	FP-CIT		IBZM			
			=	↑	↓	no
IPD (n = 127)	=	22	4	9	1	8
	↓	90	21	19	13	37
	no	15	8	5	2	–
APS[1] (n = 27)	=	4	–	–	4	–
	↓	13	2	3	7	1
	no	10	3	2	5	–
PD/APS (n = 2)	↓	2	–	1	–	1
ET (n = 22)	=	20	5	5	2	8
	↓	1	–	–	–	1
	no	1	1	–	–	–
VP (n = 16)	=	14	2	1	7	4
	no	2	1	–	1	–
DIP (n = 5)	=	4	1	–	1	2
	no	1	1	–	–	–
Other (n = 24)	=	16	5	–	1	10
	↓	4	2	–	1	1
	no	4	1	3	–	–

=: Normal FP-CIT or IBZM tracer binding ratios; ↓: tracer binding of 2 SD below healthy controls; ↑: tracer binding of 2 SD above healthy controls; no: SPECT was not performed.

[1] FP-CIT tracer binding was decreased in 7 of the 9 MSA, 4 of the 6 PSP and 2 of the 3 DLBD patients. IBZM striatal tracer binding was decreased in 10 of the 14 MSA, 6 of the 9 PSP and none of the 3 DLBD patients.

IBZM binding ratios were decreased in 10 of the 14 MSA and in 6 of the 9 patients with PSP. All 3 patients with DLBD had a normal to high striatal IBZM binding.

Finally, the diagnostic accuracy of FP-CIT and/or IBZM SPECT in this study was always higher than the accuracy of the initial probable diagnosis by the clinician before the SPECT (table 3).

Discussion

To our knowledge, this is the largest retrospective study on the diagnostic value of the FP-CIT and IBZM SPECT scan in patients with parkinsonian symptoms of unknown origin. In our study, we focused on the diagnostic delineation of IPD vs. ET, VP, DIP and APS.

Using FP-CIT SPECT to differentiate IPD from ET, we found a high OR of 82 for overall diagnostic accuracy. In this diagnostic situation, the PPV was 99%, and the NPV 48%; thus, we conclude that FP-CIT SPECT scans are sensitive in detecting IPD, but not capable of excluding IPD when negative. This is partly inherent to our study design: the low number of patients with other diseases than IPD obviously leads to a low NPV. These results are in accordance with data from a recent meta-analysis [30].

A possible explanation of the finding that 22 of 112 IPD had normal FP-CIT scans is that SPECT can be normal in early stages of disease [10–14]. In our study population, 12 of the 248 patients underwent a second FP-CIT SPECT at various time points; in these cases, accordance with the ultimate clinical diagnosis rose from 4 to 10 patients (data not shown).

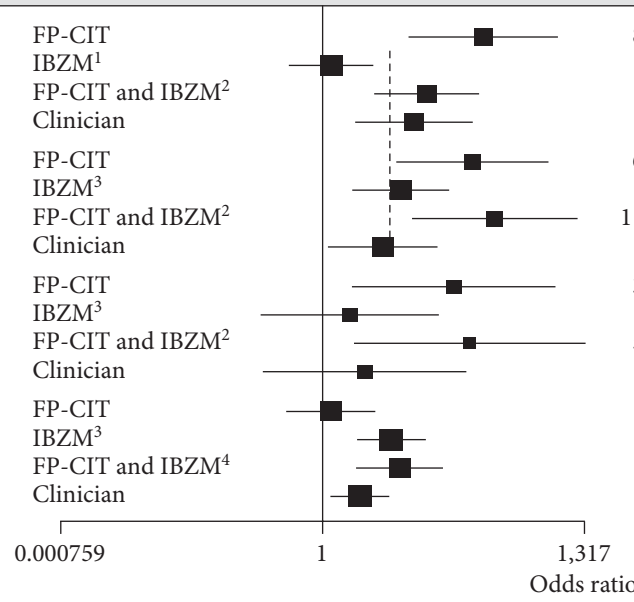
Another explanation for the relatively high number of false-negative IPD patients is the quantitative analysis of the SPECT scans. We recalculated the accuracy to differentiate patients with IPD from those with ET for visual qualitative judgment: sensitivity increased from 80 to 94%, NPV from 48 to 71%, specificity and PPV stayed unchanged. This is in accordance with recent data from Marshall et al. [31].

All patients with VP had a normal FP-CIT SPECT binding. IBZM SPECT scan was normal to high in 4 and decreased in 8 patients with VP. Our results are in agreement with the study by Tzen et al. [32], who found normal presynaptic radiotracer binding in VP. However, others found VP patients with decreased both presynaptic and postsynaptic radiotracer bindings [33–35]. These conflicting results probably reflect the controversy surrounding the diagnostic criteria of VP [26]. Future studies in this field should include well-defined patient populations and a brain MRI scan to give additional information about vascular lesions in the basal ganglia and within basal ganglia-cortical projections. Theoretically, FP-CIT and IBZM binding is expected to be normal in VP patients when clear vascular lesions in the basal ganglia have been excluded. Moreover, SPECT scans in these cases should be interpreted visually, to appreciate the abnormal pattern of receptor uptake that is probably typical for VP.

Our 5 DIP patients had normal FP-CIT scans. This is in agreement with the studies by Burn and Brooks [36] and Lavalaye et al. [37]. Hypothesizing that DIP is primarily a postsynaptic problem [38], one would expect IBZM SPECT to yield lower binding ratios. We could not confirm this as we found 2 normal and one abnormal IBZM SPECT in this population. As we could not retrieve information on the medication at the moment of the scan, we do not feel comfortable to draw firm conclusions from this small sample.

Table 3. Accuracy of FP-CIT, IBZM-SPECT, combination of FP-CIT and IBZM and initial probable diagnosis of the clinician to predict clinical diagnosis after follow-up.

Differentiation between parkinsonian subgroups	Predictor	OR (95% CI)	Sensitivity, %	Specificity, %	PPV %	NPV %
PD versus ET (n = 127, n = 22)	FP-CIT	82	80	95	99	48
	IBZM[1]	1	59	46	87	15
	FP-CIT and IBZM[2]	17	92	58	92	58
	Clinician	12	76	80	98	22
PD versus VP (n = 127, n = 16)	FP-CIT	61	80	100	100	39
	IBZM[3]	8	80	67	94	33
	FP-CIT and IBZM[2]	110	92	90	98	64
	Clinician	5	76	63	96	15
PD versus DIP (n = 127, n = 5)	FP-CIT	36	80	100	100	15
	IBZM[3]	2	80	50	97	6
	FP-CIT and IBZM[2]	56	92	100	100	28
	Clinician	3	76	50	99	1
PD versus APS (n = 127, n = 27)	FP-CIT	1	80	24	87	15
	IBZM[3]	7	80	62	87	50
	FP-CIT and IBZM[4]	8	79	69	91	44
	Clinician	3	76	47	84	35



Clinician signifies initial probable diagnosis of the clinician.

[1] True positives: IPD patients with decreased or increased IBZM binding ratios. True negatives: ET patients with normal IBZM SPECT.

[2] True positives: ET, VP and DIP patients with normal FP-CIT and normal (or decreased) IBZM binding ratios. True negatives: IPD patients with all other SPECT combinations.

[3] True positives: IPD patients with normal or increased IBZM binding ratios. True negatives: VP, DIP and APS patients with decreased IBZM binding ratios.

[4] True positives: APS patients with a combination of normal FP-CIT and decreased IBZM binding or a combination of decreased FP-CIT as well as decreased IBZM binding ratios. True negatives: IPD patients with all other combinations.

Using SPECT scans to delineate IPD from APS gave disappointing results in our study for FP-CIT, IBZM as well as the combination of both SPECT scans. With only 62% of the APS patients having decreased striatal postsynaptic tracer binding, but also 20% of the IPD patients, the specificity and NPV of IBZM are relatively low.

The literature on this is somewhat conflicting. There are 8 studies in which postsynaptic SPECT is fairly accurate, and these found postsynaptic receptors mainly affected in APS and normal or upregulated in IPD [39–46]. Schulz et al. [19], who investigated 32 MSA patients, found similar results as in our meta-analysis: only a significant loss in 63% of the patients with IBZM. However, a problem is that IPD, especially in later stages, can give low striatal postsynaptic radiotracer binding too. A study by Schwarz et al. [47] confirmed our finding that reduced postsynaptic tracer binding makes IPD unlikely but does not completely exclude IPD.

A major shortcoming of our study is that we did not re-examine all patients, blinded for the SPECT results. We only invited patients for who the clinical diagnosis could not be derived from the clinical records or the referring specialist. We tried to reduce bias by having two independent observers read the clinical records critically, to check if the patient fulfilled the accepted clinical criteria of one of the parkinsonian disorders. In case of doubt, the patient was invited for re-examination. Nevertheless, all diagnoses that were not checked by an independent, blinded physician may still be biased in favor of accurate prediction by the SPECT, as these data were known by the treating physician.

Finally, a clinical follow-up is still only a surrogate gold standard [23]. Clinicopathological studies show that 2–25% of the patients with IPD are classified incorrectly in the final stage of their disease, even by specialists in movement disorders [4–6]. Comparisons between functional dopaminergic imaging and the ultimate gold standard, autopsy-proven IPD, are almost nonexistent [48, 49]. Although practically and ethically difficult, only postmortem analysis will conclusively prove whether or not the clinical diagnosis of IPD was correct in those cases.

In summary, in these 248 patients with initially unclassified parkinsonism, roughly 70% of the ordered FP-CIT scans accurately predicted the final clinical diagnosis after follow-up. In 10% of the patients, a clinical diagnosis after follow-up could not be made.

The ability to differentiate IPD from ET, VP and DIP is an additional value of the FP-CIT SPECT over the initial clinical diagnosis. However, because of the relatively high number of false-negative FP-CIT SPECT scans in IPD patients a normal FP-CIT scan does not exclude IPD.

To differentiate patients with IPD from those with APS, both FP-CIT and IBZM SPECT scans have no additional value over the initial probable diagnosis made by the clinician who ordered the SPECT scan.

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