Clinical features and dopamine transporter SPECT imaging in early parkinsonism

Suwijn, S.R.

Publication date
2021

Document Version
Final published version

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Sven Suwijn

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Sven Roman Suwijn

Schagen | [april 2021]

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This thesis was prepared at the Department of Neurology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands.

The research in this thesis is supported by a grant from Zon-Mw (project number 0-82310-97-11031), Stichting ParkinsonFonds, Parkinson Vereniging and General Electric Healthcare.

ISBN 978-94-6416-496-1
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Clinical features and dopamine transporter SPECT imaging in early parkinsonism

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen

op dinsdag 6 april 2021 te 12.00

door Sven Roman Suwijn

geboren te HILVERSUM

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Chapter 1

Introduction to early Parkinson's disease and dopamine transporter SPECT imaging

Parkinson's disease (PD) is a progressive neurodegenerative disease that is characterized by nigrostriatal cell loss, which results in motor and non-motor symptoms. The classic motor symptoms consist of bradykinesia, rest tremor and rigidity. The most common non-motor symptoms at diagnosis include sleep dysfunction (*e.g.*, sleep-maintenance insomnia, symptoms of REM sleep behavior disorder), autonomic dysfunction (*e.g.*, constipation, daytime urinary urgency, orthostatic hypotension), hyposmia, and psychiatric dysfunction (*e.g.*, depression, anxiety, hallucinations). The International Parkinson's Disease and Movement Disorders Society published the criteria for the diagnosis of PD, in which bradykinesia is the cardinal symptom, accompanied by other motor features such as tremor and rigidity and can be supported by findings of additional examinations (*e.g.,* single photon emission computed tomography (SPECT)). There should be no signs that suggest another diagnosis.[1,2]

PD is the most prevalent form of neurodegenerative parkinsonism[3] and the second most common neurodegenerative disease after Alzheimer's disease.[4] In a pooled study, the prevalence of PD was estimated to be 1.6% in people older than 65 years of age in Europe.[5] The incidence rates for PD are between 8.5 and 19 per 100.000 per year.[3]

To date, there are no disease-modifying therapies available for PD. The main treatment consists of dopamine replacement therapy with the dopamine precursor levodopa or dopamine agonists. These therapies are highly effective in reducing symptoms and may even improve quality of life in patients without bothersome disability to warrant treatment with antiparkinson medication.[6] However, with progression of the disease more frequent doses and additional medications are often needed to maintain a stable effect of the medication (*e.g.*, catechol-o-methyl transferase inhibitors, monoamine oxidase B inhibitors, amantadine). Unfortunately, it may occur that oral medication alone is not sufficient, or severe side effects arise that cannot be managed by adjusting the medication (*e.g.*, dyskinesias, impulse control symptoms, orthostatic hypotension). Advanced therapies like deep brain stimulation, continuous levodopa/carbidopa intestinal gel infusion, and continuous subcutaneous apomorphine infusion are effective therapies for advanced stages of PD.[7-9]

Other, less common, forms of neurodegenerative parkinsonism are multiple system atrophy (MSA), Lewy body dementia, progressive supranuclear palsy (PSP), and corticobasal degeneration.

Parkinsonism may also occur in a context without being caused by a neurodegenerative disease; examples are drug-induced parkinsonism, parkinsonism as a functional neurological symptom, severe major depression.[10] In these patients there are frequently signs that indicate another cause than a neurodegenerative disorder (*e.g.*, use of certain medication, inconsistencies at neurological examination).

Finally, there are disorders like essential tremor and dystonic tremor that can be mistaken for PD. In these disorders there can be signs that resemble parkinsonism, however in many of these patients, when (re-)evaluated carefully, there may not be true bradykinesia.

An accurate diagnosis in parkinsonian patients may be challenging, especially shortly after the onset of symptoms. In early stages many symptoms and signs may overlap and these may be subtle.[11-13] Often the more distinctive symptoms generally develop in a later stage of disease. Consequently, there is a considerable percentage of clinical misdiagnosis of PD up to 24-35%.[14-16] This high percentage of misdiagnosis is worrisome since patients may not get the appropriate therapy. This becomes more essential if disease-modifying therapies for PD become available. Furthermore, the impact of having a progressive neurodegenerative disorder is tremendous.[17]

For this, it may be useful to classify parkinsonism in two distinct categories; neurodegenerative parkinsonism and non-neurodegenerative parkinsonism. The difference between these types of parkinsonism is that all forms of neurodegenerative parkinsonism are characterized by progressive nigrostriatal dopaminergic cell loss. In contrast, in non-neurodegenerative parkinsonism there are no signs of progressive nigrostriatal cell loss, hence this form of parkinsonism is essentially reversible.[11] Moreover, these two groups (neurodegenerative versus non-neurodegenerative parkinsonism) of patients have a considerable different prognosis.[18]

We aimed to improve the accuracy of the clinical diagnosis or at least to identify the patients with non-neurodegenerative parkinsonism. In order to do so a valid reference standard is indispensable. The current reference standard for neurodegenerative parkinsonism is pathological examination. Considering neurodegenerative forms of parkinsonism are progressive diseases with a life expectancy at diagnosis of many years this gold standard is commonly not feasible in research. Median survival after diagnosis of PD is 9.1 years (95% CI, 7.4 to 10.9 years).[19] In patients with MSA and PSP the median survival time is shorter (8.6 and 5.0 years, respectively).[20, 21]
Consequently, there is a need for a reliable in-vivo reference standard to improve accuracy of the clinical diagnosis to reduce misdiagnosis and to ensure the right patients are included in clinical trials.

Since the early 1990s it is possible to visualize the presynaptic dopaminergic system through imaging of the dopamine transporter (DAT) with techniques like SPECT.[22] A DAT SPECT scan is performed by intravenous administration of a small amount of a radiolabeled ligand that binds to the so-called DAT protein. This protein complex is mainly located at the terminals of the dopaminergic neurons in the basal ganglia (putamen and caudate nucleus). The degree of binding indirectly measures the number of neurons in the substantia nigra that project to the basal ganglia. In patients with PD, over 50% of the dopamine producing neurons have been affected at the onset of motor symptoms.[23] DAT SPECT imaging in early PD, and even in subjects with premotor neurodegenerative parkinsonism, shows clear deficits.[24]

DAT imaging may be considered a reference standard to detect nigrostriatal degeneration ante-mortem. For this reason, we conducted a systematic literature review on the accuracy of DAT SPECT imaging in detecting nigrostriatal cell loss and thus discriminate between patients with neurodegenerative parkinsonism and reversible parkinsonism/non-parkinsonism. Furthermore, we evaluated the accuracy of the assessment of DAT SPECT scans in clinical practice (Chapters 2 and 3) since previous reports were mainly derived from tertiary referral hospitals.[25] More specific, we focused on ^{123}I-FP-CIT SPECT scans,

since this technique is commonly used in routine practice to assess DAT expression in living human brain.

Unfortunately, very little is known about the indications for which physicians (mostly, but not exclusively, neurologists) request DAT SPECT imaging (*i.e.,* ^{123}I-FP-CIT SPECT imaging). We therefore performed a survey among Dutch neurologists to gain better insight in the indications and use for DAT SPECT imaging in routine clinical practice (Chapter 3).

As briefly mentioned above, the most commonly used radioligands in DAT SPECT imaging, ^{123}I-FP-CIT SPECT and ^{123}I-β-CIT SPECT, bind predominantly to the DAT. However, there is also some binding to the serotonin transporter (SERT). In animal studies there are signs that subjects with higher serotonin availability and higher SERT-to-DAT ratios developed more motor complications like dyskinesias. In chapter 4 we evaluated if, based on DAT and SERT availability and SERT-to-DAT ratios, ^{123}I-β-CIT SPECT imaging is associated with the onset of dyskinesias.

It can be challenging, and it is not always possible, to distinguish the different neurodegenerative causes of neurodegenerative parkinsonism (*e.g.*, PD, MSA, PSP) in early stages. In previous studies it was shown, using ^{123}I-β-CIT SPECT, that midbrain SERT availability in patients suffering from MSA was significantly reduced compared to PD.[26,27] In chapter 5, we evaluated if the final diagnosis of PD versus MSA after a long-term follow-up correlated with SERT availability and SERT-to-DAT ratios as assessed by ^{123}I-β-CIT SPECT.

Finally, we hypothesized that in patients with a neurodegenerative form of parkinsonism DAT SPECT imaging is abnormal considering the significant loss of dopamine producing neurons at the onset of motor symptoms. So, patients with clinical parkinsonism, but a normal DAT scan, may be misdiagnosed. Most of these patients have a clinical diagnosis of PD and in that case these scans are also called *"scans without evidence of dopaminergic deficit"* (SWEDD). In previous studies 4.7-14.7% of the patients with a clinical diagnosis of PD had a SWEDD.[28-30]

Therefore, in a large cohort of drug-naïve patients with a clinical diagnosis of PD we tried to reliably identify patients investigated if specific clinical features are useful to distinguish patients with nigrostriatal degeneration from those that have no nigrostriatal degeneration (SWEDD) based on the assessment of a video with a comprehensive (Parkinsonian) neurological examination and using ^{123}I-FP-CIT SPECT as a reference standard. The findings of this study results are presented in chapter 6.

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Accuracy of DAT SPECT imaging in patients with early Parkinson's disease

Chapter 2

The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism

S.R. Suwijn
C.J. van Boheemen
R.J. de Haan
G. Tissingh
J. Booij
R.M.A de Bie

European Journal of Nuclear Medicine and Molecular Imaging Research
2015:17;5-12

Abstract

Purpose

In specialized movement disorder centers, Parkinson's disease (PD) is wrongly diagnosed in 6-25% of cases. To improve the accuracy of the clinical diagnosis it is necessary to have a reliable and practical reference standard. Dopamine transporter (DAT) single photon emission computed tomography (SPECT) imaging might have the potential (high diagnostic accuracy and practical to use) to act as reference standard in detecting nigrostriatal cell loss in patients with (early-stage) parkinsonism. We performed a systematic review to evaluate if DAT SPECT imaging can be used as such.

Methods

Relevant studies were searched in the MEDLINE and EMBASE databases. Studies were selected when they met the following criteria: (1) all patients were adults with a clinical diagnosis of PD or clinically uncertain parkinsonism and (2) the study reported original data. In addition studies needed to fulfil one of the two following criteria; (A) patients underwent at least one DAT SPECT and had a neuropathological confirmed diagnosis; (B) patients underwent at least two DAT SPECT scans, performed at least two years apart.

Results

The search identified 1649 articles. Eight studies fulfilled our selection criteria and were included in this review. There was only one study including patients with diagnostic uncertainty. Sensitivity and specificity of DAT SPECT imaging to detect nigrostriatal cell loss was 98%. The other studies included patients with a diagnosis of PD in whom there was no uncertainty. In these studies sensitivity was 100%.

Conclusion

Our systematic review indicates that DAT SPECT imaging seems to be accurate to detect nigrostriatal cell loss in patients with parkinsonism.

Introduction

Parkinsonism is a clinical syndrome characterized by bradykinesia and at least one of the following symptoms: rest tremor, muscular rigidity and postural instability. Parkinsonism is most commonly caused by idiopathic Parkinson's disease (PD).[1,2] However, parkinsonism is also a prominent feature in for example progressive supranuclear palsy (PSP), multiple system atrophy (MSA), psychogenic parkinsonism, dementia with Lewy bodies (DLB), vascular parkinsonism and drug-induced parkinsonism. There is no definite test to confirm the cause of parkinsonism in clinical practice, except for the vascular causes of parkinsonism. Therefore diagnostic criteria have been developed in the past 20 years.[3-6] Although the diagnosis is straightforward when patients have a classic presentation, establishing the cause of parkinsonism can be challenging, especially in early stages.[7,8] In specialized movement disorder centers, PD is wrongly diagnosed in 6-25% of cases.[4,9-11] General neurologists may even make a misdiagnosis up to 35%.[7] In a community based study in Wales, only 53% of patients, treated with anti-parkinson medication in primary care, met the Queen Square Brain Bank criteria for the clinical diagnosis of PD when re-examined by an experienced movement disorder specialist.[12]

The different causes of parkinsonism can be classified into two distinct groups; diseases with nigrostriatal cell loss (*e.g.,* PD, MSA, PSP, DLB) and diseases without nigrostriatal cell loss (*e.g.,* psychogenic parkinsonism, dystonic tremor, dopa-responsive dystonia and drug-induced parkinsonism). This classification is of clinical importance since the prognosis is considerably worse in parkinsonism characterized by loss of nigrostriatal cells.[13] Patients without nigrostriatal cell loss, except for dopa-responsive dystonia, do not benefit from treatment with dopaminomimetics and require different treatment.[5,13,14]

The current gold standard of parkinsonism is pathological evaluation. Although accurate, it is not a practical standard for the validation of new screening methods because the time between diagnosis and death is often decades. Therefore, there is a need for an alternative in-vivo reference standard to detect nigrostriatal dopaminergic cell loss in patients with parkinsonism.

Several different diagnostic tools have been evaluated in their ability to detect nigrostriatal cell loss. The most widely used tests are dopamine transporter single photon

emission computed tomography (DAT SPECT), [^{18}F]DOPA positron emission tomography (PET) and transcranial sonography (TCS).

Tests used in establishing the cause of Parkinsonism

PET is a radiotracer-based method that can assess the in vivo function of the dopaminergic and other neurotransmitter systems. [^{18}F]DOPA PET is a reliable tool to establish nigrostriatal cell loss but not very practical in clinical practice because the technique is only available in a limited number of centers, is expensive, and expertise in cerebral PET imaging is essential.[21,22]

DAT SPECT imaging — a practical, less expensive and more widely available technique than [^{18}F]DOPA PET — has been incorporated in most centers as diagnostic tool.[23,24] DAT tracers like [^{123}I]FP-CIT are typically used. Recent studies have shown that DAT SPECT imaging might be a sensitive method to establish nigrostriatal dopaminergic degeneration.[25-30] For example, people with subclinical and even preclinical PD already have clear deficits of the nigrostriatal pathway.[27,31-34] Also, if the scan does not show a nigrostriatal deficit, it is highly unlikely that the patient suffers from symptoms caused by nigrostriatal cell loss.[11,35,36] SPECT with tracers labeling postsynaptic dopamine $D_{2/3}$ receptors (*e.g.,* [^{123}I]Iodobenzamide or [^{123}I]Iodobenzofuran) show a relatively low diagnostic accuracy, 59-80% sensitivity and 46-50% specificity in differentiating PD from non-neurodegenerative diseases.[37]

Hyperechogenicity in the area of the midbrain has been consistently found in 79-90% of patients with PD using TCS.[33,38-42] However, in 6-12% of healthy volunteers hyperechogenicity of the substantia nigra is also found. [39,42,43] This is even higher (16%) in patients with essential tremor.[44]

To summarize, DAT SPECT imaging appears to be the most suitable candidate to act as reference standard in detecting nigrostriatal cell loss in patients with (early-stage) parkinsonism. Therefore, we performed a systematic review to assess the diagnostic accuracy of DAT SPECT imaging.

Methods

Literature search

We searched the electronic databases MEDLINE and EMBASE using the entire time scale up to July 2013. Both search strategies are included in appendix 1. Furthermore we searched the reference lists of all relevant articles to identify additional published studies for possible inclusion in the review. We did not impose any language restrictions.

Selection of studies

The list of titles and abstracts were screened by two independent reviewers (SRS and CVB) for eligible studies. We had anticipated that there are only a few studies with DAT SPECT imaging and neuropathological evaluation as reference test available. Therefore we also included studies that used a second DAT SPECT scan as surrogate reference standard at least two years after the baseline DAT SPECT scan. Studies were selected according to the following inclusion criteria: (1) all patients were adults with a clinical diagnosis of PD or clinically uncertain parkinsonism. (2) The study reported original data; In addition studies needed to fulfil one of the two following criteria; (A) patients underwent at least one DAT SPECT during their life and had post-mortem neuropathological evaluation; or (B) patients underwent at least two DAT SPECT scans, performed at least two years apart.

The interval of two years was chosen to make sure the second DAT SPECT scan would detect any nigrostriatal cell los. With an annual decline of 5.5 -7.1% of dopaminergic neurons in PD and even more in atypical parkinsonian syndromes, a scan at least two years later would show a marked decline if nigrostriatal cell loss was present but not visible on the baseline scan.[29,45]

All study designs were included, with the exception of case reports, case series (less than 5 patients) and case-control studies. We did not impose restrictions regarding the type of radiotracer used. If investigators published several reports based on data from a single study population, we selected the most complete report. Articles were excluded if information on diagnostic accuracy (*e.g.,* sensitivity, specificity) could not be derived from the data and could not be obtained from the authors. In all cases, disagreements about

study selection were resolved by consensus and a third reviewer (JB) was consulted if disagreement persisted.

Data extraction and risk of bias

Data were extracted by two reviewers (SRS, CVB) independently using an extraction form designed for this review. We extracted data on the diagnostic accuracy of the studies, the baseline characteristics of studied patients (*e.g.,* disease duration, age at imaging, Hoehn and Yahr score, Unified Parkinson's Disease Rating Scale score). We also extracted data on the SPECT technique; which radiotracer was used, handling of DAT interfering medication, patient preparation, test interpretation, technical failures, and assessors (*e.g.,* knowledge of other test results). Results were compared and discrepancies between the two reviewers were resolved in a meeting.

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS 2) checklist was used to assess the methodological quality of the included studies. The QUADAS 2 tool is structured in a series of questions which should be answered 'yes', 'no', or 'unclear', and aims to evaluate the risk of different types of bias.[46]

Statistical analysis and data synthesis

For each study, patient and study characteristics were summarized using descriptive statistics. Diagnostic accuracy was described in terms of sensitivity and specificity rates with their 95% confidence intervals (CI). We did not perform a meta-analysis because we included a heterogeneous group of patients with a clinical diagnosis of PD as well as with clinically uncertain parkinsonism in this review. This alters the spectrum of disease and non-disease in the population, which may have strong impact on test accuracy.

Results

Literature search and study selection

Figure 1 shows the results of the MEDLINE and EMBASE search and the study selection. We identified 2239 articles. After duplicate removal 1649 remained. A total of 1632 articles were excluded because they did not fulfil our selection criteria. The large majority of these studies were excluded because they did not employ multiple DAT SPECT scans or

neuropathological evaluation. Seventeen articles were selected for further review. Of these, five were excluded because the study population overlapped with more complete or more recent publications. We contacted the authors of five additional studies that had missing data.[47-51] One author responded.[51] The other four articles were excluded. In the end, eight studies fulfilled our selection criteria.

Study characteristics

The characteristics of the included studies are shown in Table I. The eight included studies involved a total of 235 patients. There was only one study that assessed patients with clinically uncertain parkinsonism,[55] all other studies included patients with a clinical diagnosis of PD (five studies) or pathologically proven PD (two studies). The mean disease duration at first SPECT imaging ranged from 2.4 to 7.9 years.

Two studies used pathological evaluation as the reference standard.[52,53] The other six studies used a second DAT SPECT scan, at least two years later, as surrogate reference standard.[26,28,29,54-56] The studies using pathological evaluation were retrospective studies. All but one of the studies that used a second DAT SPECT scan were prospective studies.

Figure 1. Flowchart of eligible studies

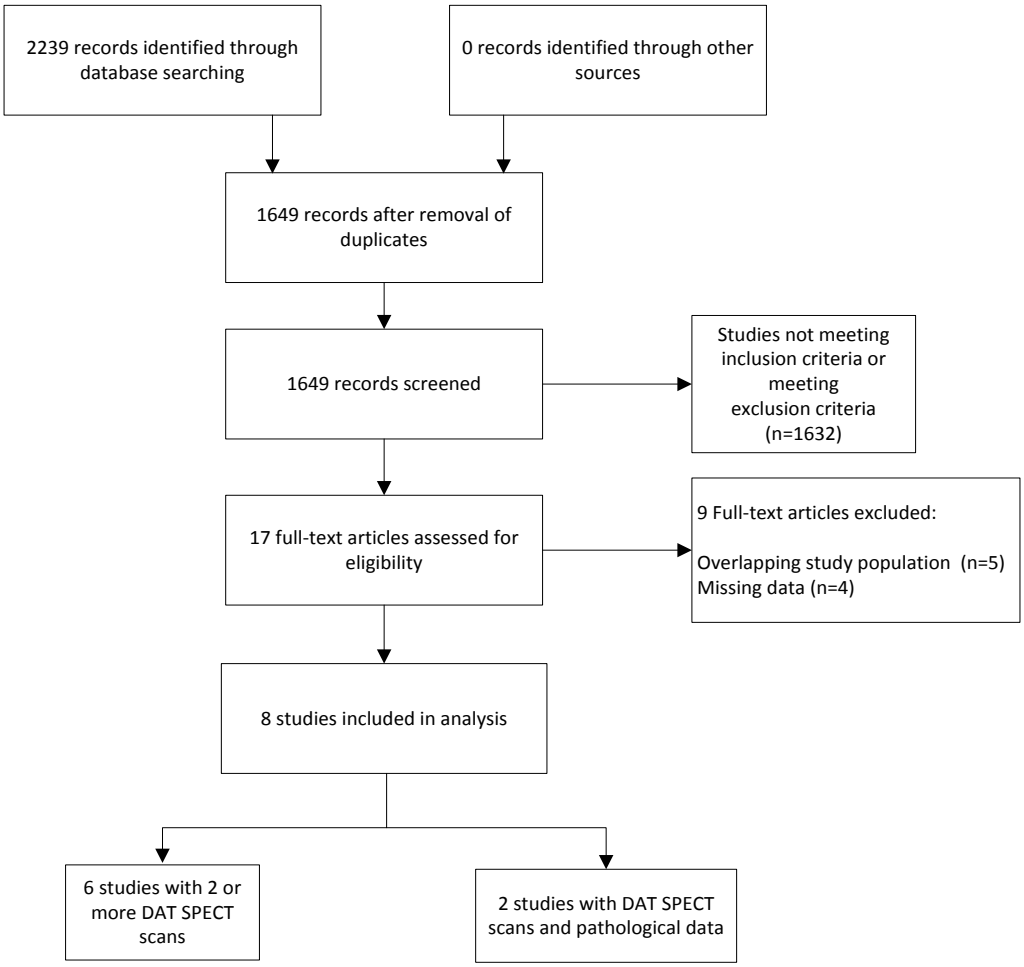

Table 1. Patient and study characteristics

Author, year	Number of patients	Target population	Inclusion criteria	Prospective or retrospective?	Reference standard	Mean disease duration at 1st scan (y±SD)	Mean age at imaging (y±SD)	Mean Hoehn and Yahr score	Mean UPDRS motor score at imaging (OFF state, 0-108)	Mean follow-up between scans (y+SD)	Radiotracer	SPECT judged visually, template or drawn	Drug stopped appropriate before SPECT?	SPECT judged blindly for results of reference standard?
Chouker, 2001	8	Clinical PD	Step 1+2 UKPDS criteria +responsedopa minomimetics	prospective	2nd DAT SPECT	3.6¥, 1-6*	57.0, 40-76*	2.0±0.8	-	2.0	IPT	template	unclear	unclear
Marek, 2001	32	Clinical PD	Step 1+2 UKPDS criteria	prospective	2nd DAT	2.5¥±2.4	60.0±11.7	1.8±0.7	18.2±8.7	2.3±0.9	beta	drawn	unclear	yes
Pirker, 2002	36	Clinical PD	Step 1+2 UKPDS criteria	prospective	2nd DAT SPECT	4.7¥±2.9	60.0±11.0	2.1±0.4	-	2.2±0.3	beta	drawn	yes	yes
Marshall, 2009	99	Clinically uncertain parkinsonism	Step 1 UKPDS criteria	prospective	2nd DAT SPECT	2.4ǂ	60.8±4.8	1.5±0.3	9.6±1.3	3.0	fpcit	visual	yes	yes
Isaias, 2010	13	Clinical PD	Step 1-3 UKPDS criteria	prospective	2nd DAT SPECT	5.0¥±2.8	63.4±8.5	-	17.2±6.0	3.2±1.0	fpcit	template	yes	unclear
Perju-Dumbrava, 2012	8	Pathologically proven PD	Neuropathological diagnosis of PD + DAT scan during lifetime	retrospective	Pathological evaluation	4.1¥±4.8	68.0±7.2	-	-	3.7±3.0ɖ	beta	drawn	unclear	unclear
Colloby, 2012	12	Pathologically proven PDD	McKeith criteria + DAT scan during lifetime	retrospective	Pathological evaluation	7.9¥±6.3	70.8±4.3	-	35.8±11.9	3.3±1.7ɖ	fpcit	template	unclear	unclear
Eggers, 2012	27	Clinical PD	Step 1-3 UKPDS criteria	retrospective	2nd DAT SPECT	3.9¥	61.7±11.2	-	25.9±5.2	2.5±0.7	fpcit	template	yes	yes

PD Parkinson's Disease, SD standard deviation, UPDRS Unified Parkinson's disease rating scale, beta [^{123}I] ß-carboxymethyoxy-3-beta-(4-iodophenyl) tropane, fpcit [^{123}I]-fluoropropyl-carbomethoxy-3ß-4-iodophenyltropane, IPT ^{123}I-N-(3-iodopropen-2-yl)-2 -carbomethoxy-3ß-(4-chlorophenyl) tropane, SPECT Single photon emission computed tomography, CI confidence interval, PDD parkinson's disease dementia, DAT dopamine transporter, UKPDS United Kingdom Parkinson's Disease society

* Full range instead of standard deviation
¥ Disease duration calculated from diagnosis
ǂ Disease duration calculated from first symptoms
ɖ In this study the interval is referring to the time between DAT SPECT imaging and pathological evaluation

Risk of bias

The risk of bias in the included studies is shown in Table 2. Most studies had at least one design flaw. Five out of the eight studies had an unclear or a high risk of bias regarding patient selection due to a poor description of patient recruitment. In three out of eight studies there was a concern regarding patient flow. There was a selection of patients that received the reference standard. In two studies, we found previous reports with more patients than the ones selected. However, the reasons for exclusion of the extra patients were not mentioned in the manuscript. In four of the eight studies it was unclear if the assessor of the index test was blinded for the results of the reference test and/or clinical diagnosis.

Table 2. Risk of Bias as assessed with the Quadas-2 tool

STUDY	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Chouker, 2001	+	?	?	+	+	+	+
Marek, 2001	?	+	+	-	+	+	+
Pirker, 2002	+	+	+	+	+	+	+
Marshall, 2009	+	+	+	+	+	+	+
Isaias, 2010	?	?	?	-	+	+	+
Perju-Dumbrava, 2012	-	?	?	+	+	+	+
Colloby, 2012	-	?	?	+	+	+	+
Eggers, 2012	-	+	+	-	+	+	+

+Low Risk - High Risk ? Unclear Risk

Diagnostic accuracy

In the only study in patients with clinically uncertain parkinsonism a high diagnostic accuracy of DAT SPECT imaging was observed with sensitivity and specificity rates of 98%. Only in two out of 99 patients DAT SPECT results at follow-up differed compared to the initial DAT SPECT scan [55]. In the other seven studies — that included patients with a clinical or neuropathological diagnosis of PD — DAT SPECT imaging had sensitivity rates of 100%. In six of these seven studies, specificity rates could not be calculated as the reference tests indicated all patients had nigrostriatal cell loss. In the study of Marek and

colleagues 30 patients showed nigrostriatal cell loss at imaging and two did not. Sensitivity and specificity rates were both 100%. An important finding of all seven studies is that the results did not change in the course of 2.0-3.7 years.

Discussion

Our study indicates DAT SPECT imaging may be accurate in detecting the loss of nigrostriatal dopaminergic cells. As anticipated, there are only two studies having both DAT SPECT imaging and pathological evaluation. None of these studies performed DAT SPECT imaging in early-stage clinical PD or in patients with clinically uncertain parkinsonism. However, these two studies show that DAT SPECT imaging at medium-long disease duration (4.1 – 7.9 years) is able to detect nigrostriatal cell loss.[52,53]

A limitation of this review is that the majority of included studies performed serial DAT SPECT imaging in patients with a high suspicion of PD. These studies were designed to measure disease progression. In one of the studies two patients had a negative reference standard. In the other studies, all included patients had a positive reference standard and consequently specificity rates of the index test could not be calculated. However, these results are in line with the only study that evaluated the diagnostic accuracy in patients with clinically uncertain parkinsonism (sensitivity and specificity 98%).

Another limitation is that in four studies it is not clear whether the investigators judging the SPECT images were blinded for signs and symptoms or for the reference standard.

Other (systematic) reviews on the accuracy of DAT SPECT imaging showed somewhat lower sensitivity (79-100%) and specificity (80-100%).[24,57,58] These reviews used the clinical diagnosis at follow-up as reference standard. The clinical diagnosis is accurate in 65 - 94% of the patients compared to the final pathological diagnosis.[4,9-11] The accuracy of the clinical diagnosis increases with the duration of symptoms.[55,59] However, most studies and clinical trials use the clinical diagnosis 3-36 months after the initial diagnosis as reference standard. The inaccurate reference standard might explain that the accuracy of DAT SPECT imaging is somewhat lower in these studies.

To improve the accuracy of the clinical criteria for PD, a reliable and practical reference standard is needed.[17-20] The current gold standard, pathological evaluation, is accurate

however not very practical to use to evaluate the accuracy of the clinical criteria because the time between the clinical diagnosis and pathological diagnosis is typically long.

For clinical trials it will be better and more practical to have an accurate in-vivo reference standard to ensure no patients with other diagnoses are included. If disease-modifying therapies become available it will also be desirable to identify patients as early as possible, maybe even in a premotor phase.[15,16] Especially considering that using the clinical criteria, based on motor symptoms more than 50% of the dopamine producing neurons are lost.[15,16]

It seems that DAT SPECT imaging could be used as an in-vivo reference standard to detect nigrostriatal cell loss and evaluate new diagnostic (screening) methods. However, considering only one study included patients with diagnostic uncertainty more diagnostic accuracy studies are needed to confirm this finding.

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Appendix 1: Search strategy

MEDLINE

Line #	Terms
1	(DAT adj SPECT).ti,ab.
2	(dopamine adj3 SPECT).ti,ab.
3	"dopamine active transporter".ti,ab.
4	(DT adj2 SPECT).ti,ab.
5	(FP-CIT adj3 SPECT).ti,ab.
6	"single photon emission computed tomography".mp.
7	dopamine.mp.
8	6 and 7
9	exp Tomography, Emission-Computed, Single-Photon/
10	exp Dopamine/
11	9 and 10
12	Beta-CIT SPECT.ti,ab.
13	1 or 2 or 3 or 4 or 5 or 8 or 11 or 12
14	exp Tomography, Emission-Computed, Single-Photon/
15	exp Dopamine/
16	exp Dopamine Plasma Membrane Transport Proteins/
17	15 or 16
18	14 and 17
19	(123I adj5 SPECT).ti,ab.
20	animals/ not humans/
21	exp Parkinson Disease/ or parkinson*.ti,ab.
22	exp "Sensitivity and Specificity"/
23	specificit*.tw.
24	accuracy.tw.
25	false negative.tw.
26	22 or 23 or 24 or 25
27	pathology.mp or exp pathology/
28	(dopamine* adj2 degeneration$).tw.
29	(post-mortem adj2 diagnosis).tw.
30	exp autopsy/
31	necrops$.tw.
32	obduction$.tw.
33	((post mortem or postmortem) adj2 examination).tw.
34	(Braak$ adj2 stage$).tw.
35	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	13 or 18 or 19
37	21 and 36
38	26 or 35
39	36 and 38
40	37 not 20
41	39 not 20
42	40 and 41

EMBASE

Line #	Terms
1	(DAT adj SPECT).ti,ab.
2	(dopamine adj3 SPECT).ti,ab.
3	"dopamine active transporter".ti,ab.
4	(DT adj2 SPECT).ti,ab.
5	(FP-CIT adj3 SPECT).ti,ab.
6	"single photon emission computed tomography".mp.
7	dopamine.mp.
8	6 and 7
9	exp single photon emission computer tomography/
10	exp dopamine/
11	9 and 10
12	Beta-CIT SPECT.ti,ab.
13	1 or 2 or 3 or 4 or 5 or 8 or 11 or 12
14	exp single photon emission computer tomography/
15	exp dopamine/
16	exp dopamine transporter/
17	15 or 16
18	14 and 17
19	(123I adj5 SPECT).ti,ab.
20	animal/ not human/
21	exp Parkinson's Disease/ or parkinson*.ti,ab.
22	exp "sensitivity and specificity"/
23	specificit*.tw.
24	accuracy.tw.
25	false negative.tw.
26	22 or 23 or 24 or 25
27	pathology.mp or exp pathology/
28	(dopamine* adj2 degeneration$).tw.
29	(post-mortem adj2 diagnosis).tw.
30	exp autopsy/
31	necrops$.tw.
32	obduction$.tw.
33	((post mortem or postmortem) adj2 examination).tw.
34	(Braak$ adj2 stage$).tw.
35	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	13 or 18 or 19
37	21 and 36
38	26 or 35
39	36 and 38
40	37 not 20
41	39 not 20

Chapter 3

Indications and diagnostic accuracy of visual assessment of DAT SPECT imaging in patients with early Parkinson's disease

S.R. Suwijn
C.V.M. Verschuur
M.A. Slim
J. Booij
R.M.A. de Bie

European Journal of Nuclear Medicine and Molecular Imaging Research
2019;9:63

Abstract

Purpose

To determine the reliability of visual assessment of [^{123}I]FP-CIT SPECT imaging by non-experts in dopamine transporter (DAT) SPECT imaging in patients with early drug-naive Parkinson's disease (PD). Also, we explored the indications of DAT SPECT imaging in clinical practice by neurologists.

Methods

We collected [^{123}I]FP-CIT SPECT scans of the Levodopa in EArly Parkinson's disease (LEAP) trial participants that were made prior to recruitment, as part of routine clinical work-up. All scans were reassessed by an expert in DAT imaging. A survey on the use of DAT SPECT imaging was send to all referring neurologists.

Results

The concordance of the initial local assessment and the expert reassessment was 98.7%. The survey showed that neurologists requested DAT SPECT imaging in only 73.6% of patients to differentiate between a neurodegenerative disease and non-neurodegenerative parkinsonism.

Conclusions

Visual assessment of [^{123}I]FP-CIT SPECT imaging by community nuclear medicine physicians in patients with early PD is reliable. Neurologists who request DAT SPECT scans are not always aware that the high accuracy is limited only to the differentiation between neurodegenerative and non-neurodegenerative parkinsonism. A significant portion of neurologists who request DAT SPECT scans are not always aware that the high accuracy is limited to the differentiation between neurodegenerative and non-neurodegenerative Parkinsonism as DAT SPECT cannot reliably distinguish the various Parkinsonian syndromes.

Introduction

Parkinsonism is characterized by bradykinesia accompanied by either rigidity and rest tremor, or both. Parkinsonism can be classified in two clinically relevant categories; Parkinsonism with nigrostriatal degeneration and parkinsonism or mimics with an intact nigrostriatal system.

First, the most frequent cause of Parkinsonism with nigrostriatal cell loss is Parkinson's disease (PD). Other, less common forms of neurodegenerative parkinsonism, also called atypical Parkinsonian syndromes (APS), include multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and corticobasal degeneration.

Second, non-neurodegenerative forms of Parkinsonism are disorders that are clinically established forms of parkinsonism/parkinsonism mimics but molecular imaging or autopsy shows no signs of nigrostriatal cell loss. Parkinsonism or mimics with an intact nigrostriatal system can be caused by for example medication, functional neurological symptoms, and essential tremor.[1]

An accurate clinical diagnosis of PD can be challenging and misdiagnosis is not uncommon, particularly early in the course of Parkinsonism since clinical features overlap frequently.[2] Distinguishing neurodegenerative versus non-neurodegenerative forms of parkinsonism is important considering the differences in prognosis and treatment. Neuroimaging can be a useful tool to distinguish between these two categories. Dopamine transporter single photon emission computed tomography (DAT SPECT) imaging is an accurate method to differentiate between neurodegenerative and non-neurodegenerative Parkinsonism, even at an early stage of the disease.[3] The alterations of the presynaptic dopaminergic neurons can be quite similar between PD and APS. Consequently, a DAT SPECT cannot differentiate between the different forms of neurodegenerative Parkinsonism in clinical practice.[4]

In clinical practice, DAT SPECT images are assessed by nuclear medicine physicians, radiologists or neurologists. Previous studies have shown that expertise in DAT SPECT imaging is preferred to visually assess DAT SPECT scans.[5] The focus of DAT SPECT imaging related research has been on the diagnostic accuracy and the use of DAT SPECT imaging in tertiary referral centers specialized in movement disorders. Little is known about the accuracy of its use in routine clinical practice in general hospitals.

This study evaluates the reliability of visual assessments by community nuclear medicine physicians of ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)nortropane ([^{123}I]FP-CIT) SPECT imaging of patients that took part in the Levodopa in EArly Parkinson's disease (LEAP) cohort and underwent DAT SPECT imaging prior to recruitment, as part of routine clinical practice. In addition, we present the results of a questionnaire, filled out by general neurologists, on the reasons to request DAT SPECT imaging by general neurologists.

Methods

Design

The current study is a retrospective cross-sectional cohort study of visual assessment of DAT SPECT scans of patients suspected to have PD that underwent [^{123}I]FP-CIT SPECT imaging before they were recruited in the LEAP-study. The LEAP-study was a multicenter, double-blind, placebo-controlled, randomized delayed-start trial. The aim of the LEAP-study was to investigate if early treatment with levodopa has a disease modifying effect.[6]

Study population

For the LEAP-study, patients in the Netherlands with recently diagnosed idiopathic PD using the standard clinical criteria were eligible.[7] The other inclusion criteria were a diagnosis made in the past two years; age 30 years and older; a life expectancy of more than 2 years; and no limitations in functional health for which the patient needed PD-medication.

Study procedures

For all LEAP-study participants, we determined whether they underwent [^{123}I]FP-CIT SPECT imaging prior to inclusion as part of routine clinical work-up. We attempted to obtain all [^{123}I]FP-CIT SPECT scans. All institutions acquired and reconstructed the images according to guidelines on DAT SPECT imaging published by the European Association of Nuclear Medicine.[8] Nuclear medicine physicians without extensive expertise in in DAT SPECT imaging (non-experts) in the referral hospitals assessed the scans, and [^{123}I]FP-CIT

SPECT scans that were evaluated by visual assessment only were included. Subsequently, the [^{123}I]FP-CIT SPECT scans were visually reassessed by an expert DAT SPECT reader (JB). The expert assessor was blinded for the results of the initial assessment by the "non-expert" and clinical details aside from the date of birth, and that the patients were participating in the LEAP-study. The images were analyzed in a familiar and consistent color scale on a HERMES workstation.

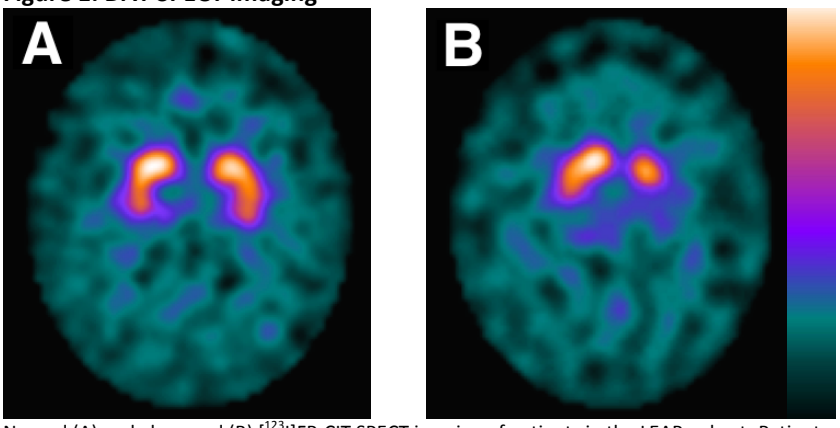
Classification and outcome of [^{123}I]FP-CIT SPECT

The [^{123}I]FP-CIT SPECT images were classified as either 'normal' or 'abnormal'. 'Normal' DAT SPECT imaging was characterized by clear binding of the radiotracer in the putamen and caudate nuclei both bilaterally, mostly symmetrical. The striata often looks circular- or oval-shaped (figure 1).[9] The result of DAT SPECT imaging was considered 'abnormal' when low binding was visual in the striatal area, in most cases asymmetrical and lower in the putamen than the caudate nucleus. Reduced binding of the radiotracer is in the early phase of PD usually visible in the dorsal putamen and expands gradually to the ventral putamen and caudate nucleus.[9]

Use of DAT SPECT imaging in clinical practice survey

In November 2016 an electronic survey was send to all neurologists that referred patients for the LEAP-study (n=146). The questionnaire consisted of two multiple-choice questions (Figure 2). The questions were: 1. 'When do you request DAT SPECT imaging?' and 2. 'In which percentage of patients with a diagnosis of PD do you use DAT SPECT imaging?' The survey was completed anonymously.

Figure 1. DAT SPECT imaging



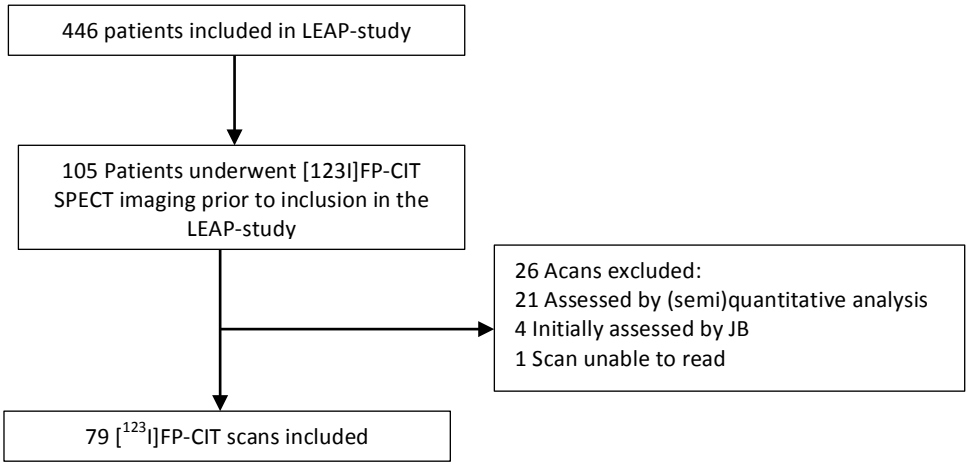
Normal (A) and abnormal (B) [^{123}I]FP-CIT SPECT imaging of patients in the LEAP-cohort. Patient A is a 64-year old male. Patient B is a 63-year old female.
DAT, dopamine transporter; SPECT; single-photon emission computed tomography; LEAP, Levodopa in EArly Parkinson's disease.

Results

Demographics

From October 2011 until May 2016 a total of 446 patients were enrolled in the LEAP-study. One-hundred-and-five of these 446 patients underwent [^{123}I]FP-CIT SPECT imaging prior to inclusion in the LEAP-study. Twenty-six scans were excluded. 21 scans were initially assessed by (semi-)quantitative analysis. Four scans were initially assessed by JB. One scan could not be reassessed due to an outdated computer system in one of the referring hospitals. A total of 79 DAT SPECT scans were included in this study (Figure 3). SPECT was performed 3-4 hours after intravenous injection of [^{123}I]FP-CIT (mean amount 185 MBq, range 140-214 MBq). The patient characteristics can be found in Table 1.

Figure 3. Flowchart of included DAT SPECT scans



LEAP, Levodopa in EArly Parkinson's disease; DAT, dopamine transporter; SPECT, single-photon emission; computed tomography; JB, J. Booij

Table 1. Demographic and clinical characteristics.	Patients (n=79)
Age – years	63.4 ± 9.9
Male sex – number (%)	52 (65.8)
Symptom duration at imaging (mean±SD) – years	1.8 ± 1.5
UPDRS[11] motor score at imaging (0-108) (mean±SD)	18.2 ± 9.4

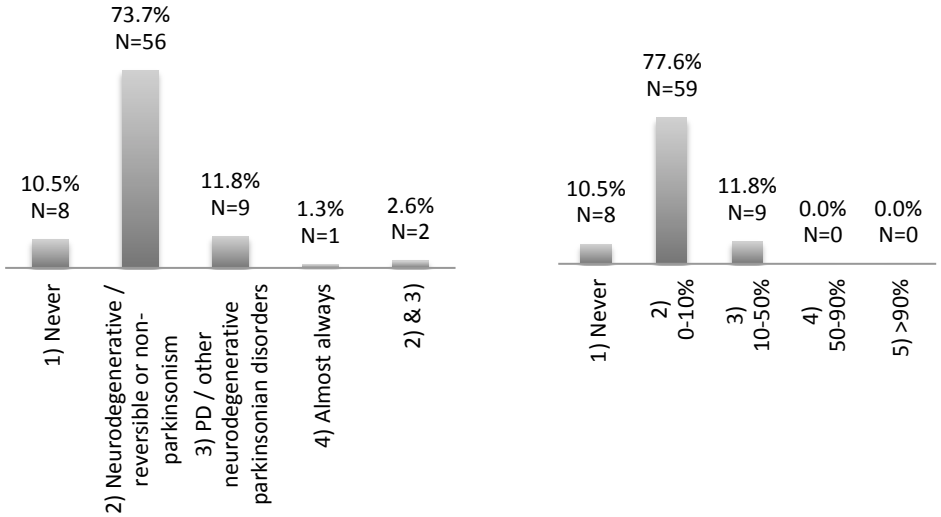
SD standard deviation, *UPDRS* Unified Parkinson's Disease Rating Scale.

Analysis

[^{123}I]FP-CIT SPECT imaging was performed in 30 hospitals (five tertiary referral hospitals and 25 community hospitals). Different dual-headed SPECT cameras and one brain-dedicated SPECT system were used. The initial assessment was "normal" in one patient and "abnormal" in 78 patients. The expert assessment was 'normal' in two patients and

'abnormal' in 77 patients. The concordance of the non-experts of the referring hospitals and JB on 'normal' versus 'abnormal' scans in this study was 98.7%.

Figure 2. Results 'Request of DAT SPECT imaging' survey
(1) In which case do you request DAT SPECT imaging? (left panel)
(2) How often do you request DAT SPECT imaging? (right panel)



DAT, dopamine transporter; SPECT, single-photon emission computed tomography; PD, Parkinson's disease; N, number of respondents.

Use of DAT SPECT imaging survey

Seventy-six neurologists responded to the questionnaire (response rate 52%). 73.6% requested DAT SPECT imaging to differentiate between a neurodegenerative and non-neurodegenerative form of parkinsonism. 11.8% of the neurologists use DAT SPECT imaging to differentiate between PD and APS (figure 2).

Discussion

Our findings are in line with the high diagnostic accuracy of visual assessments of DAT SPECT imaging in patients with a clinical diagnosis of early PD. In addition, we showed this is also true in routine clinical practice compared to a highly trained nuclear medicine physician dedicated to DAT imaging.

The strength of this study is that we evaluated the reliability of the visual assessments performed in clinical practice by nuclear physicians with various levels of expertise in neuroimaging in patients with a clinical diagnosis of early-stage PD. It was shown that false positive (abnormal) outcomes occur more frequently among less experienced observers, while experienced observers classify [^{123}I]FP-CIT SPECT scans correctly using visual assessment only.[5] Our findings suggest that this does not seem to be an issue in clinical practice, considering only one scan was found to be false positive by the expert. A limitation of this study is the selection bias. Our results reveal little about the accuracy of assessments of normal DAT SPECT scans considering the patients were already included in the LEAP-study. The LEAP-study population is not a typical population in that only patients were included in which the referring neurologist was fairly confident the patient had a diagnosis of PD. Consequently, the rate of abnormal DAT SPECT scans is considerably higher compared to routine clinical practice, therefore our results may not be applicable to general use.

A possible limitation is that only one expert reassessed the images. Nevertheless, the inter-agreement of visual assessment of DAT SPECT imaging by experts, reported in the literature is very high (Cohen's κ 0.87-0.99).[10]

Furthermore, our survey showed that most of the responding neurologists request for [^{123}I]FP-CIT SPECT imaging for an appropriate indication.[3] However, a significant portion (11.8%) of the responding neurologists request [^{123}I]FP-CIT SPECT imaging to differentiate between PD and other APS, although DAT SPECT imaging cannot reliably discriminate between neurodegenerative Parkinsonian disorders in routine clinical practice.[4] It is essential for clinicians who apply for [^{123}I]FP-CIT SPECT imaging to have knowledge of the limitations and the information it can provide. With this survey, we gained an unique insight in the use of DAT SPECT imaging by neurologists in clinical practice.

Conclusion

In conclusion, visual assessment of DAT SPECT imaging by non-experts in patients with a clinical diagnosis of early-stage PD is reliable. A significant portion of neurologists who request DAT SPECT scans are not always aware that the high accuracy is limited to the differentiation between neurodegenerative and non-neurodegenerative Parkinsonism as DAT SPECT cannot reliably distinguish the various Parkinsonian syndromes.

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Dopamine and serotonin transporter SPECT imaging in patients with early Parkinsonism

Chapter 4

Serotonin and dopamine availability in early Parkinson's disease and correlation with the development of dyskinesias

S.R. Suwijn
H.W. Berendse
C.V.M. Verschuur
A. Winogrodzka
R.M.A. de Bie
J. Booij

European Journal of Nuclear Medicine and Molecular Imaging Research
2013;3:44

Abstract

Background

Although the treatment of Parkinson's disease (PD) is very effective, in the course of the disease 40-60% of patients develop dyskinesias. The pathophysiology of dyskinesias is still unclear. Results of preclinical research suggest that uptake and uncontrolled release of dopamine by serotonergic neurons is an important factor. Based on this model, we hypothesized that dyskinesias will develop predominantly in PD patients with a relatively preserved serotonergic system.

Methods

Between 1995 and 1998 fifty patients with early-stage, untreated PD, diagnosed according to clinical criteria and reduced striatal [^{123}I]β-CIT SPECT binding were recruited. To test our hypothesis, we retrospectively assessed baseline [^{123}I]β-CIT SPECT scans for striatal dopamine transporter (DAT) and midbrain serotonin transporter (SERT) availability as well as the SERT-to-DAT ratios. We compared these data between patients that developed dyskinesias and patients that did not develop dyskinesias during a mean follow-up of 14.2 years.

Results

Approximately half of the PD patients developed dyskinesias. No differences in baseline [^{123}I]β-CIT DAT availability, SERT availability, or SERT-to-DAT ratios were found between the dyskinetic and non-dyskinetic group. The development of dyskinesias was most strongly associated with age-of-onset (P = 0.002).

Conclusion

SERT-to-DAT ratios in early-stage, untreated PD do not correlate with the future development of dyskinesias. However, our study does not exclude the possibility that SERT-to-DAT ratios increase with disease progression in patients that develop dyskinesias because of a slower rate of degeneration of the serotonergic system.

Introduction

Parkinson's disease (PD) is the second most common form of neurodegenerative diseases.[1] A key neuropathological characteristic of PD is a severe loss of dopamine-producing neurons in the brainstem, which induces several core motor features such as bradykinesia and rigidity. The development of levodopa is a milestone in the treatment of PD, since it is inexpensive and very efficacious.[2] Levodopa is converted to dopamine which replenishes the stores of endogenous dopamine and induces a fast and significant improvement in motor function.[3] Due to disease progression patients require higher daily dosages of levodopa to produce a stable clinical effect. Frequently, disabling side-effects, in particular dyskinesias, occur.[4] After 5 years of levodopa treatment, approximately 30-40% of patients suffer from dyskinesias, increasing to 40-60% after 10 years of treatment.[5,6] Nevertheless, the pathophysiology of dyskinesias is still unknown. There is a clear need for a better understanding of the pathophysiology, which may yield novel targets to develop improved treatment strategies.

In the brain, the pathway that projects from the substantia nigra to the striatum is the most prominent dopaminergic pathway. The central serotonergic system originates in the raphe nuclei. Within this nuclei complex, the dorsal raphe nucleus projects predominantly to cortical areas and the striatum.[7] PD is not only characterized by dopaminergic degeneration, but also by serotonergic degeneration.[8,9] Preclinical research has led to the development of a model that has the potential to explain the development of dyskinesias.[10] This model postulates that an imbalance between dopamine and serotonin plays a crucial role in the development of dyskinesias. More specifically, the model presumes that in early-stage PD sufficient dopaminergic neurons exist to regulate and release dopamine adequately. As the disease progresses the number of dopaminergic neurons declines. The loss of serotonin neurons, however is relatively mild compared to the loss of dopamine neurons.[8, 13] Terminal of serotonergic neurons in the striatum can also take up, store and release dopamine, yet these neurons lack auto-regulatory feedback mechanisms of dopaminergic neurons to release dopamine adequately (serotonergic neurons lack D_2 auto-receptors and dopamine transporters).[11,12] As a result of the lack of these mechanisms, dopamine release from serotonin nerve terminals in PD

may be poorly regulated, resulting in uncontrolled, excessive swings in dopamine release (called release of “false transmitter”).

In line with the model described above, studies in dopamine-depleted rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated non-human primates have shown that the removal of serotonin neurons and/or reduction of serotonin activity by serotonin agonists resulted in a significant decrease of dyskinesias.[10,14] More specifically, blockade of serotonin neuron activity by combination of 5-HT1A agonists prevented the unregulated dopamine release by central serotonergic neurons and consequently prevented the development of dyskinesias in dopamine-depleted rats.[15]

Furthermore, an increase in the incidence of dyskinesias has been observed in dopamine-depleted rats that received a transplant containing relatively many serotonin and few dopamine cells, whereas the dyskinesias decreased when rats received a transplant consisting predominantly of dopaminergic neurons.[16] An increase of dyskinesias was also observed in two PD patients who received a graft with a high striatal serotonin/dopamine transporter ratio. Moreover, administration of a serotonin 1A receptor agonist (buspirone) significantly reduced the severity of dyskinesias in both patients.[17]

Hypothesis

All in all, particularly the results of the preclinical studies suggest that dyskinesias may predominantly develop in PD patients with a relative spared serotonergic system. This study aims to determine whether an imbalance between the loss of dopaminergic and serotonergic neurons precedes the development of dyskinesias in PD. Therefore, we retrospectively assessed striatal dopamine transporter (DAT) and midbrain serotonin transporter (SERT) availability as well as the SERT-to-DAT ratios, as measured with [^{123}I]β-CIT (a radiotracer that binds to both the DAT and SERT [18]) SPECT in drug-naïve early-stage PD patients. We compared these data between patients who had developed dyskinesias and patients who had not developed dyskinesias during a minimum of five year follow-up. We expected that PD patients who had developed dyskinesias would have baseline [^{123}I]β-CIT SPECT scans with higher SERT-to-DAT ratios.

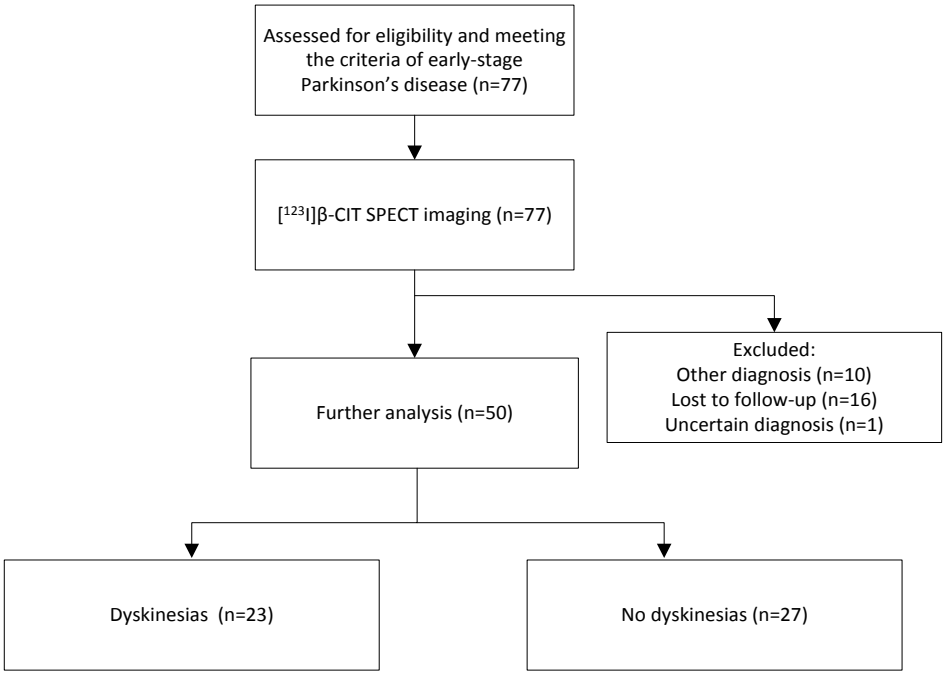
Materials and methods

Subjects

A total of 77 patients with early-stage, untreated PD, diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDSBB) clinical diagnostic criteria[19] and reduced striatal [^{123}I]β-CIT SPECT binding at the time of the initial clinical diagnosis were recruited from the outpatient clinic for movement disorders at the VU University Medical Center (VUMC) between 1995 and 1998. 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. Furthermore, all medical records were reviewed to ensure none of the patients was taking serotonergic medication at the time of SPECT imaging. At the time of diagnosis, the Beck Depression Inventory scale was used to ensure none of the patients had signs of a major depressive disorder. PD patients with dementia at baseline were not included; a Mini-Mental State Examination score below 26 was used as an exclusion criterion. Disease duration was based on the dates of the clinical diagnosis by a neurologist and the last contact during follow-up. The onset of dyskinesias was defined as the first time the neurologist reported the presence of dyskinesias. All subjects gave written informed consent to the research protocol, which was approved by the local medical ethical committee of the VUMC. The ethical review criteria conformed to the declaration of Helsinki.

In ten patients out of the total group of 77 patients, the clinical diagnosis was changed during follow-up, as previously reported[20], and these were excluded from the present study (Fig. 1). All patients were followed for at least five years. 16 patients were lost to follow-up and one had an uncertain diagnosis, leaving a group of 50 patients for further analysis.

Figure 1. Flowchart of enrolment



SPECT imaging

SPECT imaging was performed using a brain-dedicated system, the SME 810X system (Strichmann Medical Equipment Inc., Medfield, MA, USA). This system consists of 12 individual crystals each equipped with a focusing collimator. The spatial resolution of this camera system is approximately 6.5 mm full-width at half-maximum, throughout the 20-cm field of view. In order to block thyroid uptake of free radioactive iodine subjects received potassium iodide orally. [^{123}I]β-CIT (specific activity >185 MBq/nmol; radiochemical purity >99%) was injected intravenously at an approximate dose of 110 MBq. [^{123}I]-labelling and acquisition were performed as described previously.[21] Image acquisition was performed 24 hours after injection. Images were corrected for attenuation and reconstructed in 3D.[22,23]

Analysis of images

For the analysis of striatal and midbrain [^{123}I]β-CIT binding, two consecutive transverse slices representing the most intense striatal and midbrain binding, were analysed. A standard anatomical region of interest (ROI) template (constructed according to a stereotactic atlas) and including regions for the caudate nucleus, putamen, whole striatum, midbrain and occipital cortex (representing non-specific binding) was placed bilaterally on the images, as previously reported.[24] Estimates of specific striatal binding were made by subtracting occipital counts from striatal counts. Specific [^{123}I]β-CIT binding ratios in striatum, caudate nucleus, putamen, and midbrain were calculated using the formula: (mean binding in ROI-mean occipital binding) / mean occipital binding. This formula is referred as binding potential nondisplaceable (BP_{ND}).[25]

Furthermore, to assess if a higher SERT/DAT ratio precedes the development of dyskinesias, we calculated ratios of midbrain BP_{ND} versus BP_{ND} assessed in the caudate nucleus, putamen, and whole striatum. We also calculated these ratios in the most affected side.[17]

Statistical analysis

The Kolmogorov–Smirnov test was applied to screen for normality. Group differences in the distribution of gender, side-of-onset and modified Hoehn and Yahr scores were analysed by means of the chi-square test. Analysis with regard to group difference in time from diagnosis until start of levodopa was analysed using the Mann-Whitney U test. Possible differences in age, age-of-onset, disease duration, time between start of levodopa and the development of dyskinesias, years of levodopa use and the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores were analysed by using the independent t-test. In addition, the UPDRS motor score was divided into two subscores that represented predominantly dopaminergic (subscore A) and non-dopaminergic (subscore B) deficiency.[26] We compared the [^{123}I]β-CIT BP_{ND} values and SERT/DAT ratios between the group with dyskinesias (PD_{DYS}) and without dyskinesias (PD_{NDYS}) using one-way Analysis of Variance (ANOVA). After transformation by means of a natural logarithm,

all but one BP_{ND} (BP_{ND} midbrain) met with the assumption of normality. We intended to perform logistic regression to assess the impact of the different variables on the chance of developing dyskinesias. Considering that the smallest group consisted of 23 patients, only two variables could be used for logistic regression. Therefore, we used the independent t-test to analyse the variables independently. All analyses were performed at a significance level of 0.05 (two-tailed). Analysis was done using the SPSS 20.0 software package (IBM SPSS Inc., Chicago, USA).

Results

Patients

The demographic and clinical characteristics are listed in Table I. Twenty-three patients (46%) developed dyskinesias and 27 (54%) did not. Twelve patients died during follow-up (10 in PD_{NDYS} and 2 in the PD_{DYS} group). The mean follow-up of the deceased patients was 11.8 years. Age-of-onset (P=0.002), disease duration (P=0.003), UPDRS motor score at the moment of imaging (P=0.008), the total follow-up period (P=0.004) and years of levodopa use (P<0.001), were significantly different between the PD_{DYS} and PD_{NDYS} groups. There were no differences regarding the other clinical characteristics.

Table I. Demographic and clinical characteristics.

	PD_{NDYS} (n=27)	PD_{DYS} (n=23)	P-value
Age-of-onset PD (mean±SD) – yr	56·8±6·8	49·7±10·9	0.002
Male sex – no. (%)	15 (56)	16 (70)	0.39
Total follow-up (mean±SD) – months	155±49	190±29	0.004
Most affected side (striatal) (right/left)	11/16	11/12	0.43
Disease duration (mean±SD) – yr	12·8±4·1	15·8±2·4	0.003
Disease duration until levodopa use (median, ICR) – yr	3·0, 4·75	2·4, 2·6	0.57
Disease duration until onset dyskinesias (mean±SD) – yr	§§	7·8±3·9	§§
Levodopa use until onset dyskinesias (mean±SD) – yr	§§	5·1±3·0	§§
Levodopa use (mean±SD) – yr	9·5±3·4	13·2±2·0	<0.001
UPDRS motor score at moment of imaging	16.9±6·4	21.4±5·1	0.008
(total range, 0-108) (mean±SD)			
Subscore A (0-88)	10.8±3·4	14.2±3·4	0.001
Subscore B (0-20)	6.1±3·9	7.2±2·8	0.25
Modified HY score at moment of imaging (1 /1.5/2/2.5)	7/3/8/9	6/1/9/7	0.79

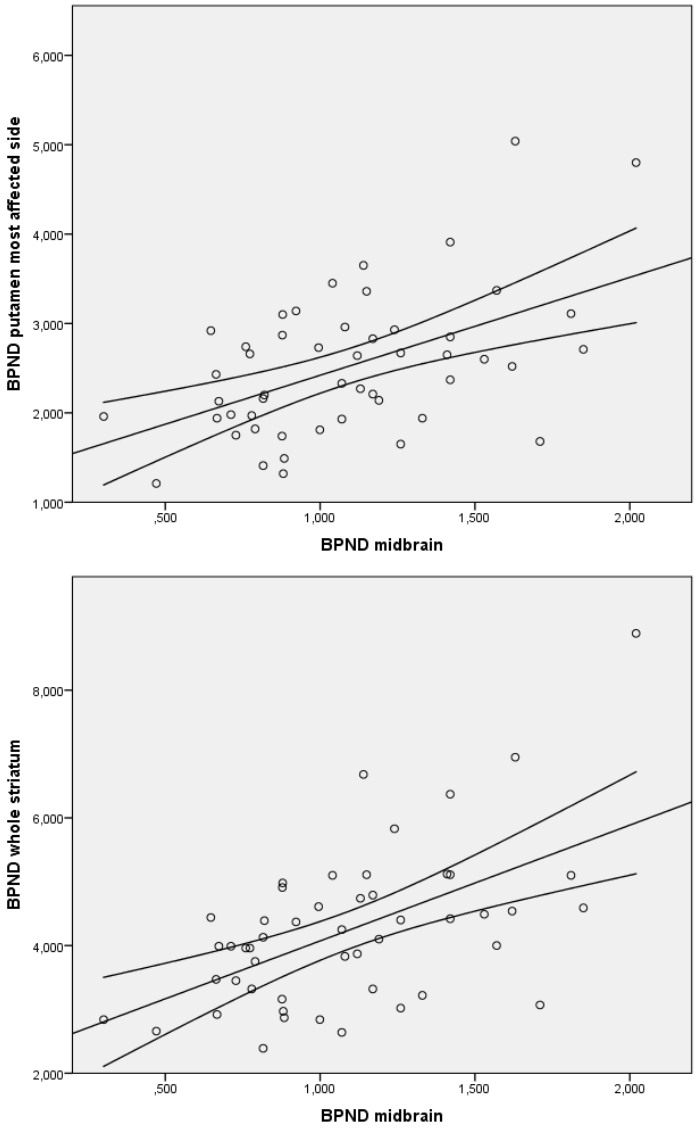
PD Parkinson's disease, PD_{NDYS} PD patients' subgroup that did not develop dyskinesias, PD_{DYS} PD patients' subgroup that did develop dyskinesias, *SD* standard deviation, ICR interquartile range, §§ data not available, *UPDRS* Unified Parkinson's Disease Rating Scale, UPDRS subscore A: consists of dopaminergic symptoms, subscore B consists of non-dopaminergic symptoms, *HY* Hoehn and Yahr

Analysis of [^{123}I]β-CIT SPECT binding

The mean [^{123}I]β-CIT BP_{ND} in the putamen was reduced compared to the caudate nucleus, the typical pattern of degeneration in PD. In the whole group, BP_{ND} in the midbrain correlated significantly (Pearson's correlation) with BP_{ND} in the most affected putamen ($r=0.265$, $p<0.001$) and whole striatum ($r=0.303$, $p<0.001$; Fig. 2).

No differences in baseline [^{123}I]β-CIT BP_{ND} were found between the PD_{DYS} and PD_{NDYS} group (Table II). This was true for BP_{ND} in the caudate nucleus, putamen, whole striatum (mean for both sides, as well as for the most affected side) and in the midbrain. Also, no significant differences between PD_{NDYS} and PD_{DYS} in SERT-to-DAT ratios were observed (Table II). Also, BP_{ND} in the caudate nucleus, putamen, striatum and midbrain did not predict the development of dyskinesias.

Figure 2. Correlation between serotonin and dopamine transporter binding.



Serotonin transporter binding (BP_{ND} midbrain) is sigificantly correlated with dopamine transporter binding in the most affected putamen (BP_{ND} putamen most affected side; left panel; $r = 0.265$, $p < 0.001$) and striatum (BP_{ND} striatum; righ panel; $r=0.303$, $p<0.001$).

Table II. Mean specific to non-specific [^{123}I]β-CIT binding ratios (BP_{ND}) (mean ± SD) and SERT-to-DAT ratios

Region of interest	PD_{NDYS} (n=27)	PD_{DYS} (n=23)	P-value
Striatum, whole	4·02 ± 0·30	4·16 ± 0·24	0·66
Striatum, most affected side	3·43 ± 0·31	3·59 ± 0·27	0·57
Caudate nucleus, whole	6·02 ± 0·30	6·33 ± 0·25	0·52
Caudate nucleus, most affected side	5·34 ± 0·34	5·73 ± 0·28	0·43
Putamen, whole	3·03 ± 0·32	3·00 ± 0·26	0·93
Putamen, most affected side	2·39 ± 0·33	2·43 ± 0·28	0·82
Midbrain	1·05 ± 0·40	1·14 ± 0·35	0·41
Midbrain/Putamen, whole	0·33 ± 0·32	0·35 ± 0·36	0·48
Midbrain/Putamen most affected side	0·42 ± 0·32	0·44 ± 0·38	0·67
Midbrain/Caudate, whole	0·17 ± 0·32	0·17 ± 0·32	0·88
Midbrain/Caudate, most affected side	0·19 ± 0·34	0·19 ± 0·37	0·97
Midbrain/Striatum, whole	0·25 ± 0·31	0·26 ± 0·34	0·75
Midbrain/Striatum, most affected side	0·29 ± 0·31	0·30 ± 0·38	0·87

SERT serotonin transporter, *DAT* dopamine transporter, *SD* standard deviation, *PD* Parkinson's disease, *PD_{NDYS}* PD patients' subgroup that did not develop dyskinesias, *PD_{DYS}* PD patients' subgroup that developed dyskinesias.

Discussion

This is the first study to assess SERT-to-DAT ratios in a relatively large cohort of drug-naive patients with early-stage PD and a mean follow-up of 14 years. During a mean follow-up of 14 years 46% of our patients developed dyskinesias, which is in accordance with the existing literature.[5,6] Patients in the PD_{DYS} group had a longer mean disease duration and

consequently had longer follow-up than patients in the PD_{NDYS} group. This could be explained by the uneven distribution of deceased patients (10 in the PD_{NDYS} and 2 in PD_{DYS} group) and the lower age-of-onset in the PD_{DYS} group. Also, at the moment of imaging, patients in the PD_{DYS} group had higher UPDRS motor scores than patients in the PD_{NDYS} group. The difference in UPDRS scores was caused by a difference in dopaminergic rather than non-dopaminergic symptoms (Table II). Interestingly, this subgroup of patients was younger at disease onset, so one can speculate that younger patients often still work and have busy lives and therefore may not notice the subtle motor signs of PD.

Our study confirms that the age-of-onset of disease is an independent risk factor for developing dyskinesias. The two groups had a mean age of PD onset of 57 (PD_{NDYS}) and 50 years (PD_{DYS}), respectively. This observation is in line with previous reports, which showed that the 5-year incidence of dyskinesias in newly diagnosed PD patients is age-of-onset dependent: 50% between the ages of 40 and 59 years, 26% between the ages of 60 and 69 years, and 16% at 70 years and older.[6] Furthermore, our patients who developed dyskinesias started on average 0.6 years earlier with levodopa compared to the PD_{NDYS} group (3.0 and 2.4 years, respectively) due to the longer disease duration, hence the difference in duration of levodopa use.

The hypothesis is that serotonergic neurons lack the feedback mechanisms of dopaminergic neurons to release dopamine adequately.[11,12] As a consequence, dopamine release from serotonin nerve terminals will be poorly regulated, resulting in uncontrolled, excessive swings in dopamine release. In contrast to this hypothesis, in the present study the dyskinesias were not preceded by a higher SERT-to-DAT ratio in patients with dyskinesias compared to non-dyskinetic patients. Our findings, however, do not necessarily reject the hypothesis that dyskinesias are associated with a relatively preserved serotonergic system. More specifically, since we performed a [^{123}I]β-CIT scan at baseline we can not exclude the possibility that a change in SERT-to-DAT ratio occurs later in the course of the disease as a result of a slower progression of the degeneration of the serotonergic system compared to that of the dopaminergic system, particularly in patients that go on to develop dyskinesias. In this regard, it is of interest that a recent study using positron emission tomography (PET) and the selective SERT tracer [^{11}C]DASB,

demonstrated a non-linear loss of presynaptic serotonergic neurons across the clinical course of PD. In the early stages of PD (disease duration shorter than 5 years) [^{11}C]DASB uptake was reduced only in the caudate nucleus, hypothalamus, thalamus and anterior cingulate cortex. In established PD (disease duration 5-10 years) the uptake was additionally reduced in the putamen, insular cortex, prefrontal cortex and posterior cingulate cortex.[27] Furthermore, in other studies loss of dopaminergic input to the putamen was severely reduced in early PD stages, while the loss of [^{11}C]DASB uptake in the putamen occurred later.[29,29] These data are in support of the assumption that serotonergic degeneration occurs at a different/slower rate in patients who develop dyskinesias compared to patients that do not.

DAT binding in PD is commonly asymmetric and the loss of binding is generally more profound in the putamen than in the caudate nucleus, which is also the case in this study, thus confirming the findings of earlier DAT SPECT studies in PD.[20,23] We hypothesized that if dopamine would be taken up predominantly by serotonergic neurons, then this phenomenon would first occur in the most affected striatal area. In other words, if high SERT-to-DAT ratios precede the development of dyskinesias, one may postulate that SERT-to-DAT ratios will be highest in the most affected putamen. However, also in this part of the striatum, SERT-to-DAT ratio was almost similar (Table II) between the two groups.

Although it is not possible to measure SERT availability in the striatum using [^{123}I]β-CIT, midbrain [^{123}I]β-CIT binding is mainly associated with the binding to SERT, while binding in the striatum is mainly associated with binding to DAT.[24] Therefore, DAT and SERT availability can be measured accurately with [^{123}I]β-CIT SPECT in different areas of the brain. However, in the present study, SERT binding in the midbrain correlated significantly with DAT binding in the most affected putamen and whole striatum (Fig. 2). This finding is in line with a previous PET study which reported a positive correlation between DAT and SERT binding in the striatum of PD patients.[30] Although such a positive correlation could not be replicated in a later smaller study,[31] this might indicate that SERT expression in the midbrain and striatum are associated. Unfortunately, in the period in which the participants were recruited and imaged, selective SERT tracers for SPECT, like [^{123}I]ADAM, were not available to assess SERT binding in the striatum.[32] On the other hand, both

[^{123}I]FP-CIT and [^{123}I]β-CIT have been used to used to image SERT and DAT in different brain areas,[23,33] though the DAT/SERT selectivity is somewhat lower for β-CIT (1.7:1 and 2.8:1, respectively), which favours the use of [^{123}I]β-CIT over [^{123}I]FP-CIT to assess extrastriatal SERT binding.[34]

Our study has both strengths and limitations. Patients were screened to exclude the presence of major depressive disorders that might have had a possible confounding effect. Furthermore, we reviewed the medical charts, with the current knowledge, to determine whether any of the patients was using a compound that may have interfered with [^{123}I]β-CIT binding at the time of diagnosis. Moreover, all scans were acquired before any dopaminergic medication was initiated to reduce possible confounding effects.

Due to the small group size (N=23) an accurate analysis using logistic regression to assess the impact of other variables (limited to two covariates) was not possible. However, the BP_{ND} in the striatal and midbrain areas were not even close to a significant difference between groups (Table II). Therefore, it is unlikely that a larger prospective study would prove that the SERT-to-DAT ratio in early-stage drug-naïve PD patients correlates with the development of dyskinesias. Another potential limitation of this study is the retrospective collection of dyskinesia data and the accompanying disadvantages thereof. However, most of the patients were closely monitored.

In conclusion, we found that the development of dyskinesias is not associated with baseline striatal DAT, midbrain SERT availability or higher SERT-to-DAT ratios. In addition, we confirmed that development of dyskinesias is age-of-onset dependent. The first finding does not support preclinical data suggesting an influence of relative sparing of the serotonergic system. However, we can not exclude that the progression of degeneration of the serotonergic system is slower in PD_{DYS} compared to PD_{NDYS}, ultimately resulting in higher SERT-to-DAT ratios at the onset of dyskinesias. Prospective imaging studies, using selective radiotracers for the SERT and DAT, are needed to shed more light on the presumed role of a relatively preserved serotonergic system in the induction of dyskinesias.

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Chapter 5

Serotonin and dopamine availability in early parkinsonism and correlation with final diagnosis

S.R. Suwijn
H.W. Berendse
C.V.M. Verschuur
R.M.A. de Bie
J. Booij

ISRN Neurology
2014:345132

Abstract

Background

Differentiating Parkinson's disease (PD) from multiple system atrophy (MSA) can be challenging especially early in the course of the disease. Previous studies have shown that midbrain serotonin transporter (SERT) availability in patients with established MSA was significantly lower compared to PD. It is unknown if this is also true for early-stage patients.

Methods

*7*7 early-stage, untreated PD patients were recruited between 1995 and 1998, underwent [^{123}I]β-CIT SPECT imaging and were followed for at least five years. 16 patients were lost to follow-up, and in 4 the diagnosis was changed to another atypical parkinsonian syndrome, but not in MSA. In 50 patients, the PD diagnosis was unchanged at follow-up. In seven patients, the diagnosis was changed to MSA at follow-up. We retrospectively assessed baseline midbrain SERT availability as well as midbrain SERT-to-striatal dopamine transporter (DAT) ratios.

Results

No difference in baseline [^{123}I]β-CIT SERT availability was found. The midbrain SERT-to-striatal DAT ratio for whole striatum was significantly lower in patients with PD compared to MSA (p=0.049). However, when adjusting for the disease duration at imaging this difference is not significant (p=0.070).

Conclusion

Midbrain SERT availability is not different between early-stage PD and MSA. Therefore, SERT imaging is not useful to differentiate between early PD and MSA.

Introduction

A key neuropathological characteristic of Parkinson's disease (PD) is loss of brainstem neurons that produce dopamine.[1] This loss induces features such as bradykinesia and rigidity. The clinical diagnosis of PD is based on the combination of motor features and response to levodopa.[2,3] Differentiating PD from multiple system atrophy (MSA) can be challenging especially early in the disease course, when signs and symptoms overlap.[4,5] Indeed, in specialized centers, PD is misdiagnosed in 6-25% of cases.[2,3,6,7] General neurologists misdiagnose PD patients in up to 35% of cases.[4] Dopamine transporter (DAT) imaging with single photon emission computed tomography (SPECT) is reliable in detecting nigrostriatal cell loss. Some studies even suggest that imaging of the DAT can provide more certainty in the differential diagnosis of PD,[8,9] although this is not supported by other studies.[10,11,19]

However, it has become clear that PD is not only characterized by dopaminergic, but also by serotonergic degeneration.[12,13] Although [^{123}I]β-carboxymethyoxy-3-β-(4-iodophenyl)tropane (β-CIT) and its fluoropropyl variant (FP-CIT) are well-known tracers for imaging of the DAT, midbrain binding of these tracers is mainly associated with binding to SERT, while binding in the striatum is mainly associated with DAT.[14-19] Therefore, both DAT and SERT availability can accurately be assessed in the same subject by analysing [^{123}I]β-CIT binding in different brain areas. The DAT/SERT selectivity is lower for [^{123}I]β-CIT (1.7:1 and 2.8:1, respectively), which favours the use of [^{123}I]β-CIT over [^{123}I]FP-CIT to assess extrastriatal SERT binding.[20]

Recently, it was shown, using [^{123}I]β-CIT SPECT, that midbrain SERT availability in patients suffering from MSA is significantly reduced compared to PD.[14,15] However, since these patients were established cases (mean disease duration of 24.0 months), it is unknown whether midbrain SERT availability is also reduced in early-stage MSA. Therefore, we assessed SERT availability, using [^{123}I]β-CIT SPECT, in patients with early-stage PD and MSA to determine whether SERT availability can be useful in differentiating early-stage PD from MSA.

Materials and methods

Subjects

77 patients with early-stage, untreated PD, diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria[21,22] and reduced striatal [^{123}I]β-CIT SPECT binding at the time of the initial clinical diagnosis were recruited at the VU University Medical Center (VUMC) between 1995 and 1998. In seven patients, the diagnosis was changed to MSA during follow-up, as previously reported.[23] All patients were followed for at least five years to ensure none of the other patients developed signs MSA or another atypical parkinsonian syndrome. 16 PD patients were lost to follow-up, two had progressive supranuclear palsy, one dementia with Lewy bodies, and one had an uncertain diagnosis, leaving 57 patients (50 PD and 7 MSA patients; Table I) for further analysis.

All subject underwent [^{123}I]β-CIT SPECT imaging prior to the initiation of dopaminergic medication. None of the subjects was on medication that could interfere with [^{123}I]β-CIT SPECT binding (*i.e.,* amphetamine or antidepressants). The medical charts were reviewed to ensure none of the patients was using serotonergic medication. Patients with dementia at baseline were not included; a Mini-Mental State Examination score below 26 was used as an exclusion criterion. At the time of the initial diagnosis the Beck Depression Inventory scale was used to identify and exclude patients with signs of a major depressive disorder. Disease duration was based on the date of the initial diagnosis established by a neurologist. All subjects gave written informed consent to the research protocol, which was approved by the medical ethical committee of the VUMC. The ethical review conformed to the declaration of Helsinki.

Table I. Demographic and clinical characteristics.

	PD (n=50)	APS (n=10)
Age-of-onset (mean±SD) – yr	54·4 ± 9·7	59·6 ± 13·1
Male sex – no. (%)	31 (62·0)	5 (50·0)
Total follow-up (mean±SD) – yr	14·2 ± 3.7	5·6 ± 3·4
Most affected side (striatal) (right/left)	22/28	5/5
Disease duration at imaging (mean±SD) – yr	1·2 ± 1·8	0·2 ± 0·1
UPDRS motor score at imaging (range, 0-108) (mean±SD)	19·0 ± 6·2	22·1 ± 6·0
Modified HY score at imaging (1/1.5/2/2.5)	13/4/17/16	2/0/2/6

PD Parkinson's disease, *APS* atypical parkinsonian syndrome, *SD* standard deviation, *UPDRS* Unified Parkinson's Disease Rating Scale, *HY* Hoehn-Yahr.

SPECT imaging

SPECT imaging was performed using a brain-dedicated system, SME 810X system (Strichmann Medical Equipment Inc., Medfield, MA, USA; Neurofocus). This system consists of 12 individual crystals each equipped with a focusing collimator. The spatial resolution of this camera system is approximately 6.5 mm full-width at half-maximum, throughout the 20-cm field of view. [^{123}I]β-CIT (specific activity >185 MBq/nmol; radiochemical purity >99%) was injected intravenously at an approximate dose of 110 MBq. [^{123}I]labelling and acquisition were performed as described previously.[24] Image acquisition was performed 24 hours after injection. Images were corrected for attenuation and reconstructed in 3D.[17,25]

Analysis of images

For the analysis of striatal and midbrain [^{123}I]β-CIT binding, representing DAT and SERT binding, respectively, two consecutive transverse slices representing the most intense striatal and midbrain binding were analysed. A standard region of interest (ROI) template (constructed according to a stereotactic atlas) and including regions for the caudate nucleus, putamen, whole striatum, midbrain and occipital cortex (representing non-specific binding) was placed bilaterally on the images, as previously reported.[17] Estimates of specific midbrain or striatal binding were made by subtracting occipital counts from striatal or midbrain counts. Specific [^{123}I]β-CIT binding ratio was calculated using the formula: (mean binding in ROI-mean occipital binding)/mean occipital binding. This formula is referred to as nondisplaceable binding potential (BP_{ND}).[26] Furthermore, we calculated BP_{ND} in the midbrain versus BP_{ND} assessed in the caudate nucleus, putamen, and striatum (midbrain SERT-to-striatal DAT ratios). All images were analyzed by one operator blinded to the clinical data.

Statistical analysis

The Kolmogorov–Smirnov test was applied to screen for normality. Midbrain BP_{ND} met with the assumption of normality only after transformation by a natural logarithm. Group differences regarding gender and side of onset were analysed using the chi-square test. Possible differences in age-of-onset, disease duration until imaging and the UPDRS motor scores were analysed using an independent t-test. We compared the [^{123}I]β-CIT BP_{ND} values and SERT-to-DAT ratios between PD and MSA using ANOVA. Logistic regression was performed to assess the impact of independent predictors. Analysis was done using SPSS 20.0 (IBM Inc., USA) at a significance level of 0.05.

Results

Patients

The demographic and clinical characteristics are listed in Table I. The two groups were different in disease duration at imaging (p=<0.005) and total follow-up (p=<0.005). There were no differences regarding the other clinical characteristics. 19 patients died during follow-up (12 PD and all 7 MSA patients).

Analysis of [^{123}I]β-CIT SPECT binding

The mean [^{123}I]β-CIT BP_{ND} was reduced in the putamen compared to the caudate nucleus in all patients. No statistical significant difference in midbrain [^{123}I]β-CIT BP_{ND} was found between the two groups (Table II). The mean SERT-to-DAT ratio (midbrain-to-whole striatum) was significantly lower in patients with PD compared to MSA (p=0.048). However, when adjusting significantly different disease duration at imaging this difference was not significant (Table III).

Table II. Mean specific to non-specific [^{123}I]β-CIT midbrain binding ratio (BP_{ND}) (mean ± SD) and midbrain SERT-to-striatal DAT ratios

Region of interest	PD (n=50)	APS (n=10)	P-value
Midbrain	1.03 ± 0.37	1.27 ± 0.52	0.129
Caudate nucleus	5.79 ± 1.84	5.53 ± 2.26	0.71
Putamen	3.15 ± 0.97	3.56 ± 1.37	0.42
Midbrain/Putamen	0.36 ± 0.13	0.46 ± 0.22	0.05
Midbrain/Caudate nucleus	0.18 ± 0.06	0.27 ± 0.13	0.001
Midbrain/Striatum	0.26 ± 0.09	0.36 ± 0.17	0.011

SERT serotonin transporter*, DAT* dopamine transporter, *SD* standard deviation, *PD* Parkinson's disease, *APS* atypical Parkinsonian syndrome

Table III. Independent predictors of diagnosis

	Constant	Midbrain–to-striatum ratio	Disease duration at imaging
β	-3.161	7.285	-2.614
p-value	0.020	0.070	0.237

β logistic regression coefficient.

Discussion

The results of this study include two important findings; (1) SERT-to-DAT ratios were not different between patients with early PD and MSA. (2) In contrast to a previous report,[15] the MSA patients in our study did not have significantly lower midbrain SERT availability compared to PD. This could be explained by the difference in disease duration between the studied populations. Scherfler and colleagues studied PD and MSA patients at a mean disease duration of 20.4 and 24.0 months, respectively. Our population was scanned at a mean disease duration of 12.3 months for PD and 2.4 months for MSA, thus at a very early disease stage. It is possible that serotonergic degeneration in MSA occurs at a different rate at later disease-stages compared to PD.

Patients with PD had a longer follow-up than patients with MSA. This could be explained by the uneven distribution of deceased patients (12 PD and all 7 MSA patients). This was expected considering the mean survival of PD is longer compared to MSA.

Our study has both strengths and limitations. Patients were screened to exclude the presence of major depressive disorders that might have had a possible confounding effect. Furthermore, we reviewed the medical charts, with the current knowledge, to determine whether any of the patients was using a compound that may have interfered with [^{123}I]β-CIT binding at the time of diagnosis. Moreover, all scans were acquired before any dopaminergic medication was initiated to reduce possible confounding effects. To our knowledge, this is the first study that assesses midbrain SERT availability in prospectively recruited patients with early-stage PD and MSA. Moreover, SPECT imaging was acquired

at a mean disease duration of 1.2 years for PD and 0.2 years for MSA, thus at a very early stage.

A possible limitation of the present study is that we used a non-selective tracer to assess both DAT and SERT. Unfortunately, in the period that the patients were recruited and imaged (*i.e.*, 1995-1998) selective SERT tracers, like [^{123}I]ADAM, were not available.[29] However, although it is not possible to measure SERT availability in the striatum using [^{123}I]β-CIT, midbrain [^{123}I]β-CIT binding is mainly associated with the binding to SERT, while binding in the striatum is mainly associated with binding to DAT.[17] Therefore, DAT and SERT availability can be measured accurately with [^{123}I]β-CIT SPECT in different areas of the brain. The DAT/SERT selectivity is lower for [^{123}I]β-CIT (1.7:1 and 2.8:1, respectively), which favours the use of [^{123}I]β-CIT over [^{123}I]FP-CIT to assess extrastriatal SERT binding.[20]

A major limitation is the number of patients with MSA (n=7) in this present study. We can therefore not exclude that in a larger prospective study midbrain SERT availability is significantly lower in early-stage MSA compared to PD. However, it is difficult to prospectively recruit MSA patients in a very early stage since these patients are often diagnosed as PD.[4,6,7] Therefore large groups of clinically diagnosed PD patients or patients with clinically uncertain parkinsonism will have to be recruited to get a substantial amount of MSA patients imaged at an early stage.

Conclusion

We found that midbrain SERT availability does not differentiate between PD and MSA patients in an early-stage. Our findings suggest that degeneration of the serotonergic system is similar in the early clinical stages of MSA and PD, but we can not exclude that degeneration of this system progresses at different rates in later diseases stages. Therefore, SPECT imaging targeting the SERT is not useful to differentiate between early PD and MSA.

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Clinical features in early Parkinson's disease

Chapter 6

Value of clinical signs in identifying patients with scans without evidence of dopaminergic deficit (SWEDD)

S.R. Suwijn
H. Samim
C. Eggers
A.J. Espay
S. Fox
A.E. Lang
M. Samuel
M. Silverdale
C.V.M. Verschuur
J.M. Dijk
H.J. Verberne MD
J. Booij
R.M.A. de Bie

Journal of Parkinson's disease
2020;10:1561-1569

Abstract

Background

In clinical trials that recruited patients with early Parkinson's disease (PD) 4-15% of the participants with a clinical diagnosis of PD had normal dopamine transporter single photon emission computed tomography (DAT SPECT) scans, also called "scans without evidence of dopaminergic deficit" (SWEDD).

Objective

To investigate in patients with a clinical diagnosis of PD, if specific clinical features are useful to distinguish patients with nigrostriatal degeneration from those that have no nigrostriatal degeneration.

Methods

We performed a diagnostic test accuracy study. Patients that participated in the Levodopa in Early Parkinson's disease trial, a clinical trial in patients with early PD, were asked to participate if they had not undergone DAT SPECT imaging earlier. The index tests were specific clinical features that were videotaped. A panel of six neurologists in training (NT), six general neurologists (GN), and six movement disorders experts (MDE) received a batch of ten videos consisting of all SWEDD subjects and a random sample of patients with abnormal DAT SPECT scans. The raters analyzed the videos for presence of specific signs and if they suspected the patient to have SWEDD. The reference test was visually assessed DAT SPECT imaging.

Results

Of a total of 87 participants, three subjects were SWEDDs (3.4%). The overall intraclass correlation coefficient (ICC) of the Parkinsonian signs was poor to moderate with ICCs ranging from 0.14 to 0.67. NT correctly identified 50.0% of the SWEDD subjects, GN 33.3%, and MDE 66.7%.

Conclusions

Our study suggests that the selected videotaped clinical features cannot reliably distinguish patients with a clinical diagnosis of PD and an abnormal DAT SPECT from patients with clinical PD and a SWEDD.

Introduction

Despite the significant advances in (nuclear) imaging and genetics to support the diagnosis of Parkinson's disease (PD) in recent years, the diagnosis of PD remains mainly a clinical one. Bradykinesia is the cardinal symptom, which must be accompanied by tremor and/or rigidity.[1-3] In order to make the diagnosis, supportive signs are often present and exclusionary signs absent. An accurate diagnosis can be challenging in early stages, particularly when the clinical features are subtle.[4, 5] Using dopamine transporter single photon emission computed tomography (DAT SPECT) imaging, patients can be classified into two distinct groups; patients with nigrostriatal dysfunction, which can be degenerative (*e.g.,* PD, multiple system atrophy, progressive supranuclear paralysis, dementia with Lewy bodies), and patients without nigrostriatal dysfunction. Among patients with clinically diagnosed PD whom are enrolled in trials or imaging studies for PD, 4-15% have been found to have normal DAT scans, also referred to as "scans without evidence of dopaminergic deficit" (SWEDD).[6, 7] SWEDD cases do not develop abnormal DAT SPECT scans on long-term follow up.[8] In contrast, in early stages of PD, and even in preclinical stages, striatal DAT binding is significantly reduced.[9-11] Previous studies however suggest that a significant proportion of SWEDD cases may be related to an incorrect visual interpretation of DAT SPECT scans, rather than or in addition to an erroneous clinical diagnosis.[12]

Reliable identification of diagnoses is paramount to individual patient care. As an adjunct, for clinical trials in early PD it is critical to ensure that the appropriate patients are included. The Levodopa in EArly Parkinson's disease (LEAP) clinical trial provided a unique opportunity to investigate if patients clinically diagnosed with early PD and nigrostriatal dysfunction can reliably be differentiated from SWEDD subjects. Using a video assessment and raters with various levels of expertise, we explored the usefulness of selected clinical features to identify SWEDD subjects.

Methods

This study was a diagnostic test accuracy study. The index tests were specific clinical features that were videotaped. The reference test was visually assessed DAT SPECT imaging. This study was ancillary to a multicenter, randomized, double-blind, placebo-

controlled trial with a delayed-start design, the LEAP trial.[13] Patients for the LEAP trial were recruited by general neurologists from 50 community hospitals and by movement disorders specialists in seven academic hospitals in the Netherlands. The LEAP clinical trial and this ancillary study were approved by the ethics committee at the Amsterdam University Medical Centers in the Netherlands. The studies were conducted in accordance with the principles of the Declaration of Helsinki.

Patients

Patients were eligible for the LEAP clinical trial if they had received a clinical diagnosis of PD within the previous two years from a neurologist who based the diagnosis on standard clinical criteria[14,15], if they had insufficient disability to warrant treatment with antiparkinson medication, if they were 30 years of age or older, and if they had a life expectancy of more than two years. Patients who had been treated previously with antiparkinson medication were excluded.

All LEAP participants were able to participate in this ancillary study unless they used medication or substances interfering with DAT SPECT imaging that could not be discontinued, in case of pregnancy, or if the patient underwent prior DAT SPECT imaging.

Study procedures

After inclusion in the LEAP clinical trial, but prior to randomization, a physical examination focused on Parkinsonism was video recorded and DAT SPECT imaging performed. There was no fixed sequence of study procedures (acquisition of the DAT SPECT scan and video recording). The results of the imaging had no influence on the participation in the LEAP clinical trial.

Physical examination

We used the following parameters to be assessed by the video panel (see supplemental file 1 for video protocol): bradykinesia defined as a decreased amplitude and/or progressive deceleration of movement,[17] re-emerging tremor in patients with a postural or rest tremor, reduced arm swing while walking, asymmetric arm swing during walking that normalizes during running, contralateral mirror movements, reduced tremor in the

most affected limb during finger tapping on the contralateral side,[18] and ten-step tandem gait test.[19]

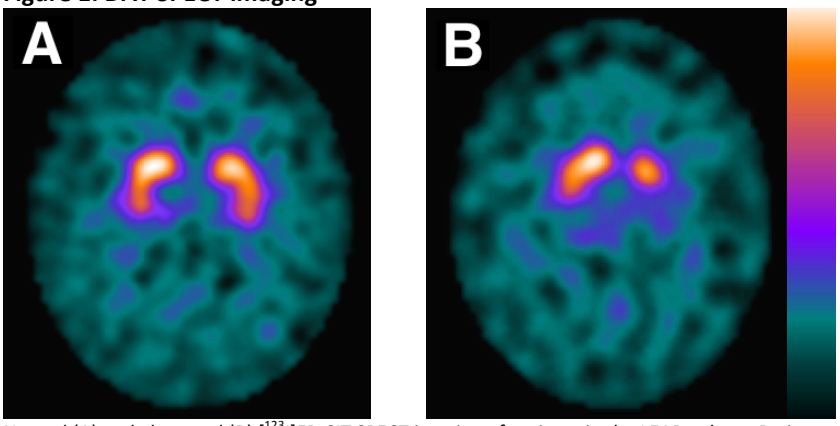
DAT SPECT imaging

DAT SPECT imaging was performed in seven hospitals (four tertiary referral hospitals and three community hospitals) in the Netherlands. Each participant was injected intravenously with approximately 185 MBq ^{123}I-N-omega-fluoropropyl-2ß-carbomethoxy-3ß-(4-iodophenyl)nortropane ([^{123}I]FP-CIT or [^{123}I]ioflupane) and images were acquired 3 hours later.[16] Patients were pretreated with potassium iodide drops or tablets according to the standard protocol of the hospital. Images were acquired on 2-headed or brain-dedicated SPECT systems. Although all centers had experience in DAT imaging for routine clinical purposes, each participating center was asked to optimize the acquisition of the images by considering the EANM guidelines regarding the acquisition of DAT SPECT scans.[20]

Classification and outcome of DAT SPECT

The DAT SPECT scans were visually assessed independently by two experts in neuroreceptor imaging (JB, HV). The experts were blinded to the initial assessment of the DAT SPECT and the clinical details aside from gender and date of birth. The images were analyzed in a familiar and consistent color scale on a HERMES workstation. The DAT SPECT images were classified as either “normal” or “abnormal”. This determination was based on the extent and intensity of the uptake of the radiotracer in the striatum. “Normal” DAT SPECT imaging was characterized by intense binding of the radiotracer in the putamen and caudate nuclei bilaterally, mostly symmetrical with almost equal intensity of the binding. Normal striatal binding looks comma- or crescent-shaped on transversal images (Fig. 1).[21] The result of DAT SPECT imaging was considered “abnormal” when a decreased binding of the radiotracer was apparent in any of the striatal areas, in most cases asymmetrically. In the early phase reduced binding of the radiotracer is usually visible in the dorsal putamen and expands to the ventral putamen and caudate nucleus.[21]

Figure 1. DAT SPECT imaging



Normal (A) and abnormal (B) [^{123}I]FP-CIT SPECT imaging of patients in the LEAP-cohort. Patient A is a 64-year old male. Patient B is a 63-year old female.
DAT, dopamine transporter; SPECT; single-photon emission computed tomography; LEAP, Levodopa in EArly Parkinson's disease.

Video assessment

Since the accuracy of video assessments of the specific symptoms may be dependent on experience,[22] we formed a video panel of assessors with different levels of expertise. Six neurologists in training (NT), six general neurologists (GN), and six movement disorder experts (MDE) individually analyzed the videos (presence of signs tested during the comprehensive neurological examination) while blinded for the DAT SPECT imaging results. An example of the case record form for the video assessment can be found in supplemental file 2. All raters received the same set of ten videos, which consisted of three SWEDD subjects and a random selection of seven patients with abnormal DAT SPECT imaging that participated in this ancillary study.

The random sample of seven videos was selected using the =RAND() formula in Microsoft Excel. This function generates a list with a random number per participant that can be sorted from low to high. The first seven subjects with the lowest numbers on the list were selected. The quality of the videos and neurological examinations were assessed (*e.g.*, sufficient lighting, socks removed, whole body was filmed during execution of UPDRS items 18, 19 and 20, and all parts of the examination were performed correctly and long enough). If a video was considered to be of insufficient quality, the following video on the list was selected until there were seven videos of sufficient quality. The assessors were

blinded for the number of SWEDD subjects, or the number of subjects with abnormal DAT SPECT imaging as well as any other clinical information.

Statistical Analysis

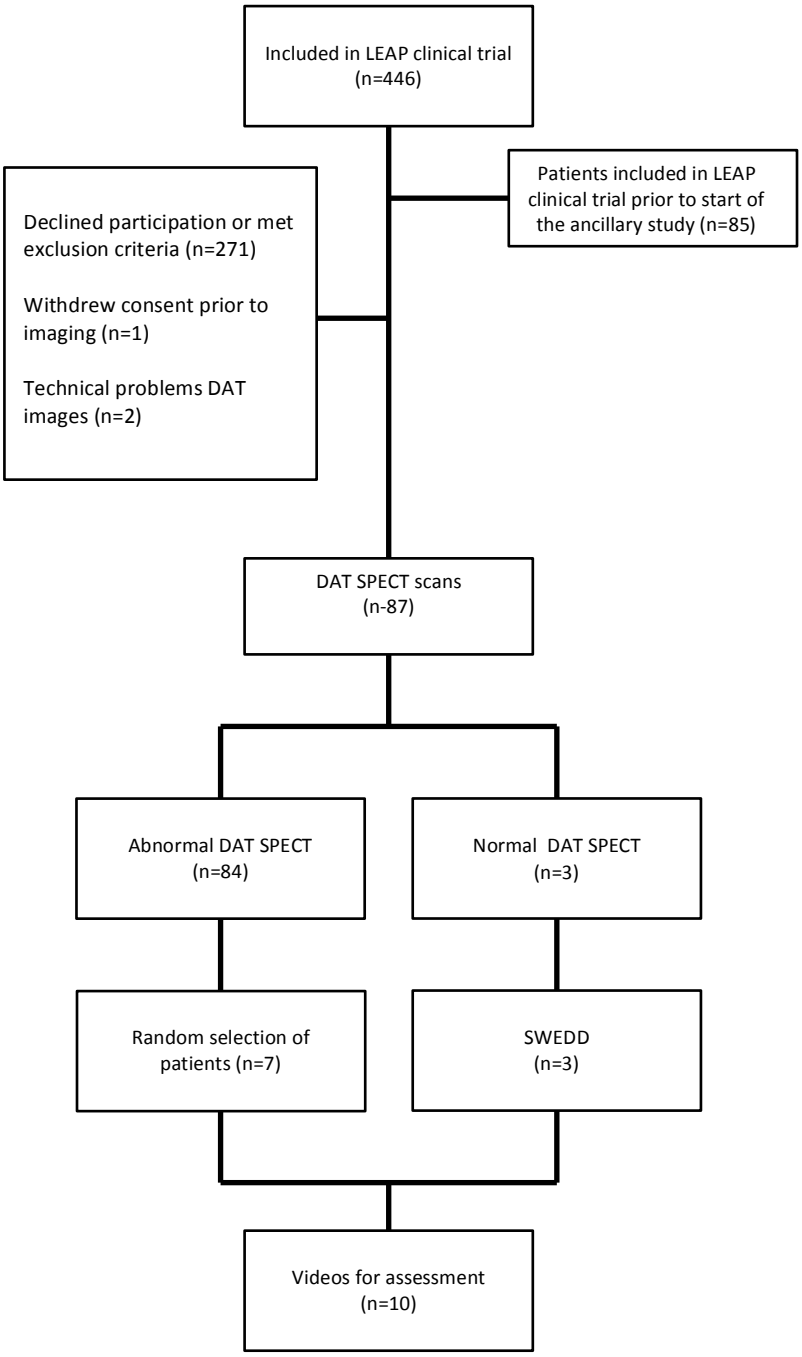
Because of the unexpected low number of SWEDD subjects, the analysis of the data was mainly qualitative with limited statistical analysis. The inter-rater reliability per item of the comprehensive neurological examination was determined by calculating the intraclass correlation coefficient. We selected the two-way mixed model and tested the absolute agreement. The single measure coefficient was used. Based on the 95% confident interval (CI) of the ICC estimate, values less than 0.50, between 0.50 and 0.75, between 0.75 and 0.90, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively.[23] Analyses were performed with the use of SPSS software, version 25.

Results

Patients

From August 2011 through May 2016, 446 patients were enrolled in the LEAP trial. The ancillary study was initiated after 85 had already been included in the LEAP trial and 271 participants declined participation or met exclusion criteria. One patient withdrew consent prior to DAT SPECT imaging and two patients were excluded due to technical issues with the DAT SPECT images. This left a total of 87 participants that underwent both DAT SPECT imaging and a videotaped examination (Figure 2). Eighty-four patients had abnormal DAT SPECT imaging. Three patients (3.4%) had normal DAT SPECT imaging, which remained normal on rescanning 80 weeks after baseline imaging. There were no discrepancies between the two experts in neuroreceptor imaging who assessed the images. The baseline characteristics and demographics are shown in Table 1.

Figure 2. Selection of LEAP patients evaluated to participate in the ancillary study


Included in LEAP clinical trial
(n=446)
Patients included in LEAP clinical trial prior to start of the ancillary study (n=85)
Declined participation or met exclusion criteria (n=271)
Withdrew consent prior to imaging (n=1)
Technical problems DAT images (n=2)
DAT SPECT scans
(n-87)
Abnormal DAT SPECT
(n=84)
Normal DAT SPECT
(n=3)
Random selection of patients (n=7)
SWEDD
(n=3)
Videos for assessment
(n=10)

SWEDD identification

One of the MDE did not fill out the question asking if he suspected the subjects to have a normal or abnormal DAT SPECT imaging due to misinterpretation of the question. Overall, SWEDD subjects were correctly identified in 41.2%. NT correctly identified 50.0% (median, range 0-70%), GN 33.3% (0-66.7%), and MDE 66.7% (0-100%) of the SWEDD subjects. The full dataset of the video assessments is provided in supplemental file 3.

Patients with abnormal DAT imaging

Overall, the assessors identified 80.7% of the patients with abnormal DAT SPECT imaging correctly. The NT identified 71.4% (median, range 57.1-85.7%) of the patients with abnormal DAT SPECT imaging correctly compared to 85.7% (median, range 71.4-100%) of GN and 85.7% (median, range 71.4-85.7%) of MDE.

In contrast, one patient (Subject 5) was overall correctly identified in only 52.9% of the assessments. Interestingly, the raters that did not find an asymmetrical arm swing while walking (88.9%), suspected the patient frequently (55.6%) of having a SWEDD, even in presence of bradykinesia.

Table 1. Baseline characteristics and demographics

	Normal DAT SPECT imaging			**Abnormal DAT SPECT imaging**
	Subject1	Subject2	Subject3	PD subjects (n=7)
Age – yr (mean±SD)	62	75	68	64.7±5.7
Gender (M/F)	Male	Female	Female	6/1
Symptom duration at imaging – (months, median, IQR)	19	12	4	12 (4-109)
Clinically most affected side (Left/Right/symmetrical)	Right	Symm.	Right	4/1/2
First symptom (tremor/bradykinesia/pain/stiffness)	T	T/B/S	B/P	5/2/1/2
Total UPDRS score (0-176, mean±SD)	19	29	22	23.7±10.4
Part I (mean±SD)	3	2	2	2.6±1.4
Part II (mean±SD)	5	9	4	7±4.2
Part III (mean±SD)	7	16	16	13.1±5.4
Part IV (mean±SD)	2	2	0	1±1.5
Beck Depression inventory-II (0-33, median, IQR)	11	15	5	7 (0-12)
Mini Mental State Examination (0-30, median, IQR)	29	30	28	29 (29-30)

SWEDD Scan without evidence of dopaminergic deficit, *PD* Parkinson's disease, *UPDRS* Unified Parkinson's disease Rating Scale, *IQR* interquartile range, *SD* Standard deviation

Table 2. Intraclass correlation coefficient with confidence intervals

	Neurologists in Training	General Neurologists	Movement Disorders Experts	Overall
eceleration of pace	0.19 (0.00-0.55)	0.26 (0.06-0.61)	0.22 (0.04-0.58)	0.26 (0.11-0.56)
cceleration of pace	0.21 (0.02-0.58)	0.08 (-0.05-0.41)	0.29 (0.07-0.66)	0.27 (0.09-0.59)
educed amplitude	0.43 (0.19-0.75)	0.16 (-0.02-0.52)	0.17 (-0.01-0.53)	0.37 (0.18-0.68)
umber of arrests	-0.02 (-0.09-0.21)	0.19 (-0.00-0.57)	0.24 (0.05-0.67)	0.15 (0.04-0.51)
andem gait	0.72 (0.49-0.98)	0.48 (0.23-0.78)	0.40 (0.14-0.77)	0.67 (0.44-0.91)
e-emerging phenomenon	0.44 (0.18-0.76)	0.71 (0.45-0.92)	0.54 (0.29-0.82)	0.62 (0.40-0.88)
symmetrical arm swing 'hile walking	0.46 (0.22-0.77)	0.56 (0.30-0.83)	0.55 (0.30-0.82)	0.52 (0.32-0.79)
ormalization arm swing 'hile running	0.13 (-0.04-0.48)	0.09 (-0.05-0.42)	0.05 (-0.05-0.33)	0.14 (0.04-0.41)
ontralateral mirror ıovement	0.16 (0.00-0.50)	0.21 (0.02-0.57)	0.29 (0.07-0.66)	0.33 (0.15-0.67)
educed tremor	0.58 (0.32-0.84)	0.45 (0.21-0.76)	0.62 (0.35-0.87)	0.54 (0.33-0.82)
licrography	0.24 (0.05-0.59)	0.30 (0.09-0.65)	0.25 (0.04-0.66)	0.36 (0.16-0.73)
nstable writing pattern	0.21 (0.01-0.58)	0.43 (0.19-0.75)	0.41 (0.14-0.80)	0.45 (0.22-0.81)
AT-deficiency	0.31 (0.08-0.66)	0.30 (0.08-0.65)	0.26 (0.03-0.63)*	0.31 (0.15-0.63)

Intraclass correlation coefficient with confidence intervals are based on five assessments instead of six

Intraclass correlation coefficient

The overall intraclass correlation coefficient (ICC) of the individual items was poor to moderate with ICCs ranging from 0.14 to 0.67 (Table 2). Re-emerging tremor (0.62, 95% confidence interval (CI) 0.40-0.88), arm swing while walking (0.52, 95% CI 0.32-0.79), reduced tremor after immobilization (0.54, 95% CI 0.33-0.82), and tandem gait test (0.67, 95% CI 0.44-0.91) were the only items with an overall ICC above 0.5. All other items had ICCs below 0.5.

Discussion

This analysis showed that video-based assessments of clinical features might be insufficient to accurately distinguish individuals with SWEDD from patients with abnormal DAT SPECT imaging. The inter-rater agreement of interpreting clinical features in patients with suspected PD is poor to moderate, independent of the level of expertise.

Our panel for the video assessment was not able to reliably differentiate SWEDD subjects from patients with neurodegenerative Parkinsonism based on videos. However, two MDE were able to identify all three SWEDD subjects correctly. One of these MDE was even able to classify all patients correctly. This rater scored the individual items of the examination similarly to the other raters, but had a different conclusion if the patient had normal or abnormal DAT SPECT imaging. This was the only patient in which the same ratings led to a different conclusion. These findings may suggest that a "custom weighted compound score" of all findings is more reliable rather than the individual features of the neurological examination. However, due to the small number of SWEDD subjects in this study it was not possible to determine whether individual items or a combination thereof were critical in correctly identifying the subjects. Furthermore, we had expected that the accuracy of SWEDD identification would increase with increasing level of expertise and experience, which was not the case.

This study showed that the overall inter-rater agreement regarding the presence or absence of clinical features is poor to moderate. In contrast to Fearon et al[22] we did not find that MDE had a higher inter-rater agreement compared to non-MDE (NT and GN).

However, we did find that NT had the lowest inter-rater agreement in 7 (out 13 items) compared to 3 for GN and MDE.

The items of the physical examination that were selected merit some discussion. Bradykinesia is one of the cardinal features of Parkinsonism so it has to be present in patients with any Parkinsonism. SWEDD subjects however may not have true bradykinesia.[17, 24] The re-emerging rest tremor is seen in the majority of patients with PD and is reported in other forms of neurodegenerative Parkinsonism. This phenomenon may be absent in SWEDD subjects.[25] Patients with PD nearly always (92%) have a reduced asymmetric arm swing during walking; this or a bilateral reduction of arm swing is recognized in about two-thirds of subjects with SWEDD.[25] We also included normalization of the arm swing while running. There is no published literature on this phenomenon. However, we observed that many PD patients with an asymmetric arm swing during walking have a normal or markedly improved arm swing while running. We hypothesized that for running a change in motor program is initiated, therefore in patients with psychogenic Parkinsonism the arm swing could remain reduced. A reduced tremor in the most affected limb during finger tapping on the contralateral side is found in patients without dopaminergic degeneration.[18] Tandem gait performance was included since patients with PD have a normal tandem gait, therefore we expected this to be abnormal in patients with a normal DAT SPECT scan.[19] The included patients were patients without impairment in daily life and therefore we hypothesized that possible patients with MSA or PSP would still have a normal tandem gait.

One of the shortcomings of this study, as with any video study, is that clinical features like rigidity cannot be appreciated, and other items assessed clinically can vary from individual to individual; *e.g.,* sequential handwriting. Furthermore, most patients were visited at home, which led to improvising to obtain the best videos possible. For example, in some cases the walking distance had to be reduced due to the living situation of the patient. Moreover, the lighting varied among the videos, which could have influenced the assessments.

"One could argue that erroneous visual assessment of DAT SPECT imaging contributes to the SWEDD percentage. However, previous studies have shown that visual assessment of DAT SPECT imaging by experts and even non-experts is highly reliable.[26,27] Additionally, all three SWEDD cases were rescanned approximately 80 weeks later, and also all three follow-up scans were rated as being normal by the two expert readers who analyzed the scans independently".

One of the strengths of this study is the fact that these were all patients who were referred to participate in the LEAP-clinical trial. To our knowledge this is the first study in which the included SWEDDs were initially referred by a neurologist who had no clinical doubt and diagnosis was made on clinical grounds only. We agree the number of SWEDDs is low, however these are the exact type of SWEDDs we wanted to evaluate.

In conclusion, our findings suggest that it is very difficult to reliably identify SWEDD subjects from patients with PD based solely on a video assessment of a neurological examination focused on parkinsonism.[6] Interestingly, the level of expertise of the video assessors did not appear to play a significant role in the inter-rater agreement as well as in the correct identification of the patients. As mentioned above the sample size was considerably smaller than anticipated, therefore we can not draw firm conclusions. Until other reliable diagnostic and mechanistic biomarkers become available, DAT imaging should be used to confirm appropriate patient selection in clinical trials on disease-modifying drugs.

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Supplementary material

Supplemental file 1. LEAP-DAS ancillary study video protocol

Please film the first page of the CRF with studynumber before initiation of the neurological examination.

Make sure there is sufficient light. Do not film against a light source. Make sure the patient does not wear socks or shoes during the examination.

Film the entire body. If this is not possible it is important that when one of the limbs moves, the contralateral inactive limb is also filmed.

Speech

Can you sit upright with your hand on your lap and feet flat on the ground without moving or speaking [film entire body during a few seconds]

"Can you tell me what you ate for dinner yesterday?"

Rest tremor

Can you place your hands on your lap, then close your eyes and say the months of the year backwards.

Spreading tremor

If the participant has a tremor try to stop it by immobilizing the affected limb [film entire body during 30 seconds]

Postural tremor

Stick out both arms with the palms down and the fingers spread slightly [10 seconds]

Action tremor

Can you, using your index finger of your right hand, go back and forth between your nose and my index finger [4 times, repeat with left hand]

Fingertapping

Stick out your right hand with your palm facing me. Keep your vinger spread and tap the index finger on the thumb as fast as possible, but with big amplitude [Stop after 10 seconds, repeat with left hand]

Open and closing fists

Stick out your right hand with your palm facing down. Open and close your hand as fast as possible [Stop after 10 seconds, repeat with left hand]

Diadochokinesis

Stick out your right hand with palm facing down. Turn your palm up and down as fast as possible [Stop task after 10 seconds, then test left hand]

Toe and foot tapping

Put your two feet next to each other flat on the floor. You can tap the ground with the right forefoot as quickly as possible while keeping your heels on the ground. [After 10 seconds stop, then left forefoot] Then put your two feet next to each other flat on the floor. You can tap the heel with the right heel, as quickly as possible, on the floor while keeping your foot on the ground [After 10 seconds stop, then left heel]

Rise

Can you rise from this chair with your feet flat on the floor and your arms in front of your chest. [If the participant is unable to perform the task you can tell to use the railing of the chair. If the participant is unable to rise with the help of the railing you can assist the participant]

Walking

Can you walk back and forth between these two points until I ask you to stop [distance between points needs to be 7 meter, let the participant walk towards the camera twice]

Running

Can you run back and forth between these two points until I ask you to stop [distance between points needs to be 7 meter. Let the participant walk towards the camera twice]

Ten step tandem gait test

Can you walk, foot by foot over this line for me [total 10 steps, film frontside]

Tone

You can place the feet about 20 to 30 centimeters apart and relax. I will move your shoulders back and forth [film whole body from left and right side]

Postural reflexes

Stand firmly with your feet slightly apart. I will try to pull you over. You must try to keep standing. If necessary, you may take a step backward, try to do this as little as possible [film whole body from the side]

Writing

Can you write a random sentence on this piece of paper [Only film the result during 5-10 seconds]

Supplemental file 2. LEAP-DAS Video Analysis CRF

Subject number |__||__||__||__||__||__||__||__||__||__||__||__|

Reviewer's name |__||__||__||__||__||__||__||__||__||__||__||__|

1. Bradykinesia

The presence of bradykinesia during the video defined as decreased amplitude and/or progressive deceleration of movements during the execution of UPDRS items 23, 24, 25 and 26.

	Yes	**No**
Deceleration of pace	☐	☐
Acceleration of pace	☐	☐
Reduced amplitude	☐	☐
Number arrests in ongoing movement	|__||__||__|	

2. Tandem gait performance (10 steps)

	Yes	**No**
Normal tandem gait test?	☐	☐

3. Re-emerging phenomenon

Did you see a re-emerging phenomenon in patients with a tremor (rest/postural) during the video and the execution of UPDRS items 20 and 21?

Yes ☐ **No** ☐ **N/A** ☐

4. Asymmetric arm swing

Did you see an asymmetric arm swing during the execution of UPDRS item 29?

Yes ☐ **No** ☐

Did you see a near identical lack of arm swing while walking and running?

Yes ☐ **No** ☐

5. Contralateral mirror movements

Did you see contralateral mirror movements in the least affected arm during the execution of UPDRS items 23, 24, 25, 26 in the most affected arm?

6. Diagnosis

Yes ☐ **No** ☐

Does this patient have an abnormal DAT-SPECT (compatible with for example Parkinson's disease)?

Yes ☐ **No** ☐

If yes: is it PD or is there a suspicion that it is an atypical parkinsonism?

PD ☐ **Atypical parkinsonism** ☐

7. Reduced tremor

Was the intensity of the tremor reduced in the affected arm(s) during the execution of UPDRS items 23, 24, 25 and 26 with the opposite limb or during mental tasks (i.e. distractibility)?

Yes ☐ **No** ☐ **N/A** ☐

8. Writing

	Yes	No
Did you see micrography?	☐	☐
Did the patient have an unstable writing pattern?	☐	☐

9. Contribution of the items to your conclusion above

Can you give a rating per item below (irrespective of it's presence or absence) as to how much it contributes to your answer on the question above? (1 being not important and 5 being very important)

	1	2	3	4	5
Progressive deceleration	☐	☐	☐	☐	☐
Reduced amplitude	☐	☐	☐	☐	☐
Number of stops during video	☐	☐	☐	☐	☐
Tandem gait performance	☐	☐	☐	☐	☐
Re-emerging phenomenon	☐	☐	☐	☐	☐
Asymmetric arm swing while walking	☐	☐	☐	☐	☐
Asymmetric arm swing while running	☐	☐	☐	☐	☐
Contralateral mirror movement	☐	☐	☐	☐	☐
Spreading tremor	☐	☐	☐	☐	☐
Reduced tremor	☐	☐	☐	☐	☐
Micrography	☐	☐	☐	☐	☐

Additional comments

Reviewer statement

	Yes	No
Did you complete all the questions on this CRF completely?	☐	☐

Date: **Signature:**

Supplemental file 3. Full results of video assessment

SWEDD 1

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No
	Acceleration of pace	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No	No	No	No	No	Yes	No
	Reduced amplitude	No	No	No	No	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes
	Number arrests in ongoing movement	2	0	0	0	0	2	2	0	2	0	2	8	2	2	0	0	8	0
2. Tandem gait performance	Normal tandem gait test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	N/A	No	N/A	N/A	N/A	No	N/A	N/A	No	N/A	N/A	N/A	No	No	N/A	N/A	N/A	No
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	No	No	Yes	No	No	No	Yes	No	Yes	No	No	No	No	Yes	No	No	Yes	Yes
	Near identical lack of arm swing while walking and running?	No	No	No	No	No	Yes	No	No	No	Yes	Yes	No	No	No	No	No	No	No
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
6. Reduced tremor	During UPDRS 23,24,25,26	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No
7. Writing	Micrography	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
	Unstable writing pattern	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
8. Diagnosis	Abnormal DAT-SPECT?	No	No	Yes	No	No	No	Yes	No	Yes	No	No	No	No	Yes	No	No	Yes	N/A
	PD OR Atypical parkinsonism?	x	x	PD	x	x	x	PD	x	PD	x	x	x	x	AP	x	x	PD	
9. Contribution of the items to your conclusion	Progressive deceleration	4	4	4	2	4	4	5	5	1	5	4	4	4	3	5	4	4	5

above

Reduced amplitude	4	4	4	4	4	3	5	5	5	4	4	2	4	3	2	4	4	3
Number of stops during video	2	3	4	1	3	2	3	3	5	3	3	2	3	2	2	1	4	3
Tandem gait performance	3	3	1	1	2	1	5	1	3	4	4	4	2	1	4	1	2	3
Re-emerging phenomenon	4	2	1	5	3	4	5	4	1	3	2	2	2	1	4	1	2	4
Asymmetric arm swing while walking	2	4	4	5	4	5	5	5	5	5	5	4	4	5	4	4	4	4
Asymmetric arm swing while running	2	3	4	5	4	3	5	4	3	4	4	2	4	2	3	1	2	2
Contralateral mirror movement	3	2	1	1	3	2	5	4	1	3	2	3	3	1	4	1	2	2
Reduced tremor	2	2	1	4	3	2	3	2	1	2	2	2	2	1	2	1	2	2
Micrography	4	3	1	3	4	3	4	5	1	4	2	3	3	1	3	1	4	5

SWEDD2

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
	Acceleration of pace	No	No	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	No	No	No
	Reduced amplitude	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Number arrests in ongoing movement	0	0	0	0	2	4	1	0	1	7	3	1	2	3	8-10	0	10	4
2. Tandem gait performance	Normal tandem gait test?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	Yes	No	N/A	N/A	N/A	Yes	N/A	No	x	Yes	No	No	No	Yes	No	N/A	N/A	No
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	Yes	Yes	No	Yes	Yes
	Near identical lack of arm swing while walking and running?	Yes	No	No	Yes	No	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
6. Reduced tremor	During UPDRS 23,24,25,26	No	N/A	N/A	N/A	N/A	N/A	N/A	No	No	No	No	No	No	N/A	No	N/A	N/A	No
7. Writing	Micrography	No	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No
	Unstable writing pattern	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	x
8. Diagnosis	Abnormal DAT-SPECT?	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	N/A
	PD OR Atypical parkinsonism?	PD	x	AP	PD	x	PD	x	PD	PD	PD	x	PD	PD	PD	x	x	x	x
9. Contribution of the items to your conclusion above	Progressive deceleration	5	2	4	4	4	5	5	5	3	5	4	4	5	5	5	3	3	4
	Reduced amplitude	5	2	4	4	4	5	5	5	5	4	3	4	5	5	2	3	3	4
	Number of stops during video	2	3	1	1	2	3	1	3	5	4	4	2	4	4	3	1	3	5

Tandem gait performance	2	3	5	1	2	1	5	1	4	2	2	2	3	4	3	1	4	3
Re-emerging phenomenon	5	4	1	1	2	3	5	4	1	4	x	4	2	5	4	1	2	2
Asymmetric arm swing while walking	2	5	4	1	4	4	5	5	1	2	2	2	2	5	3	1	4	4
Asymmetric arm swing while running	2	2	4	1	4	4	5	4	1	2	2	2	2	2	3	1	4	3
Contralateral mirror movement	2	3	2	1	2	1	5	4	1	2	2	2	2	3	3	1	2	2
Reduced tremor	2	2	1	1	2	2	3	x	1	2	2	2	2	3	2	1	2	3
Micrography	2	4	1	1	3	1	4	4	1	2	3	x	2	4	3	1	4	2

SWEDD3

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
	Acceleration of pace	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No
	Reduced amplitude	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
	Number arrests in ongoing movement	1	0	0	0	1	1	0	0	2	2	2	0	1	0	0	0	2	0
2. Tandem gait performance	Normal tandem gait test?	No	No	No	Yes	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes	No	No
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	n/a	N/A	N/A	N/A	N/A	No	N/A	N/A	No	N/A	No	N/A	N/A	No	N/A	N/A	N/A	No
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Near identical lack of arm swing while walking and running?	No	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No
6. Reduced tremor	During UPDRS 23,24,25,26	n/a	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No
7. Writing	Micrography	No	No	Yes	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes	No	No	Yes	Yes
	Unstable writing pattern	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes	No
8. Diagnosis	Abnormal DAT-SPECT?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	N/A
	PD OR Atypical parkinsonism?	AP	AP	AP	PD	AP	x	PD	PD	AP	AP	AP	AP	x	AP	x	x	AP	
9. Contribution of the items to your conclusion above	Progressive deceleration	3	4	1	5	2	3	5	5	1	4	2	2	4	4	4	x	3	4
	Reduced amplitude	3	2	1	5	4	5	5	5	4	3	4	2	3	3	3	x	3	4
	Number of stops during video	2	2	1	1	2	3	1	3	3	2	3	2	3	1	2	1	3	3

Tandem gait performance	3	4	5	1	3	4	5	1	5	3	4	5	2	4	3	1	4	2
Re-emerging phenomenon	2	1	1	1	2	1	5	4	1	2	2	2	1	1	1	1	2	4
Asymmetric arm swing while walking	4	5	3	5	4	5	5	5	3	4	4	4	3	5	3	3	4	3
Asymmetric arm swing while running	3	3	5	5	2	5	5	4	3	3	4	4	4	3	3	1	4	2
Contralateral mirror movement	2	4	1	1	2	1	5	4	3	2	2	2	2	2	1	1	2	2
Reduced tremor	1	1	1	1	2	1	3	2	1	2	2	2	2	1	1	1	2	2
Micrography	1	1	x	1	3	4	1	5	1	x	3	1	2	4	1	1	2	4

PD1

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Acceleration of pace	No	No	Yes	No	Yes	Yes	Yes	No	No	Yes	No	No	No	No	No	x	No	No
	Reduced amplitude	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Number arrests in ongoing movement	0	0	0	0	1	2	0	0	0	1	0	0	0	0	5	x	5	3
2. Tandem gait performance	Normal tandem gait test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	x	Yes	Yes
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Near identical lack of arm swing while walking and running?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	Yes	No	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	Yes	No	Yes	No
6. Reduced tremor	During UPDRS 23,24,25,26	No	No	No	No	No	N/A	No	No	No	No	No	No	No	No	No	No	No	No
7. Writing	Micrography	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
	Unstable writing pattern	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No
8. Diagnosis	Abnormal DAT-SPECT?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	N/A
	PD OR Atypical parkinsonism?	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	X	PD	PD	X
9. Contribution of the items to your conclusion above	Progressive deceleration	5	4	3	5	4	4	5	5	3	5	2	4	4	4	4	5	4	5
	Reduced amplitude	5	4	4	5	4	4	5	5	5	5	4	3	4	4	3	5	4	4
	Number of stops during video	2	2	1	1	2	4	1	4	1	2	x	1	2	3	3	1	3	4

Tandem gait performance	4	1	5	1	2	1	5	1	4	2	x	4	3	3	2	1	2	3
Re-emerging phenomenon	5	5	2	1	2	1	5	4	5	4	4	3	4	3	2	3	2	4
Asymmetric arm swing while walking	5	5	5	5	4	5	5	5	5	5	5	4	4	4	2	4	4	4
Asymmetric arm swing while running	3	5	5	5	4	5	5	4	5	2	5	x	4	5	2	1	4	3
Contralateral mirror movement	5	2	4	1	3	5	5	4	3	3	2	2	3	2	3	1	3	3
Reduced tremor	1	2	1	1	2	3	3	x	1	2	2	2	2	2	2	1	3	2
Micrography	2	2	1	1	2	1	4	4	1	x	2	2	2	2	4	x	2	4

PD2

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	No	No	No	No	No	Yes	Yes	No	No	yes	No	No	No	Yes	Yes	No	No	Yes
	Acceleration of pace	No	No	No	Yes	No	No	Yes	No	No	No	No	Yes	Yes	Yes	No	No	Yes	No
	Reduced amplitude	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Number arrests in ongoing movement	0	0	0	0	0	3	0	0	0	0	0	x	0	1	2	0	4	2
2. Tandem gait performance	Normal tandem gait test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	x	Yes	Yes	Yes	Yes
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	Yes	No	N/A	No	N/A	No	Yes	No	No	Yes	No	Yes	No	Yes	No	Yes	Yes	No
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Near identical lack of arm swing while walking and running?	No	No	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	Yes	No	No	No	No	Yes	Yes	Yes	No	No	No	No	No	No	No	x	No	No
6. Reduced tremor	During UPDRS 23,24,25,26	No	N/A	N/A	No	No	No	No	No	No	No	No	No	No	Yes	No	x	Yes	No
7. Writing	Micrography	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	x	No	No
	Unstable writing pattern	Yes	No	Yes	No	No	Yes	No	Yes	No	Yes	No	No	No	No	No	x	Yes	No
8. Diagnosis	Abnormal DAT-SPECT?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A
	PD OR Atypical parkinsonism?	PD	X	AP	AP	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	X
9. Contribution of the items to your conclusion above	Progressive deceleration	2	4	1	1	2	3	5	5	1	3	2	2	2	3	5	3	3	4
	Reduced amplitude	2	4	1	1	3	5	5	5	1	3	2	4	4	3	3	3	4	3
	Number of stops during video	2	2	1	1	3	3	1	3	1	2	2	2	2	3	2	1	3	3

Tandem gait performance	2	2	5	1	2	1	5	1	4	2	2	4	2	2	3	1	2	2
Re-emerging phenomenon	5	4	1	1	2	2	5	4	1	4	2	4	2	4	2	2	4	4
Asymmetric arm swing while walking	5	2	5	1	4	2	5	5	5	4	2	4	4	5	4	2	3	4
Asymmetric arm swing while running	2	4	1	1	3	2	5	4	5	3	2	4	4	3	4	1	2	2
Contralateral mirror movement	4	2	1	1	2	4	5	4	1	2	2	2	2	2	1	1	2	2
Reduced tremor	1	2	1	1	2	3	3	2	1	2	2	2	2	4	1	1	4	2
Micrography	3	4	1	1	2	1	4	5	1	2	2	1	3	3	1	1	2	5

PD3

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	No	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	No	No	Yes
	Acceleration of pace	No	x	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes	No
	Reduced amplitude	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Number arrests in ongoing movement	0	0	1	0	3	1	1	2	2	3	4	2	1	0	12-14	0	11	4
2. Tandem gait performance	Normal tandem gait test?	No	Yes	Yes	Yes	Yes	x	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	Yes	No	N/A	n/a	N/A	No	N/A	N/A	No	N/A	n/a	No	No	No	No	No	N/A	No
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No
	Near identical lack of arm swing while walking and running?	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	no	Yes	No
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
6. Reduced tremor	During UPDRS 23,24,25,26	n/a	N/A	N/A	n/a	N/A	No	N/A	N/A	No	N/A	No	Yes	N/A	N/A	No	No	N/A	No
7. Writing	Micrography	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No
	Unstable writing pattern	No	No	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
8. Diagnosis	Abnormal DAT-SPECT?	No	Yes	No	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	N/A
	PD OR Atypical parkinsonism?	x	AP	x	x	x	AP	x	x	AP	PD	AP	AP	x	PD	x	x	x	x
9. Contribution of the items to your conclusion above	Progressive deceleration	4	2	3	3	3	3	5	5	1	4	5	3	3	5	5	1	3	4
	Reduced amplitude	2	5	3	3	3	5	5	5	5	4	3	3	3	5	2	3	4	4
	Number of stops during video	3	2	3	3	2	3	1	3	5	2	3	2	3	2	4	1	3	4

Tandem gait performance	2	2	2	3	2	4	5	1	4	x	2	2	4	2	2	1	4	3
Re-emerging phenomenon	3	2	1	3	2	1	5	4	1	2	2	3	2	1	2	2	3	4
Asymmetric arm swing while walking	4	4	1	3	4	4	5	5	3	4	2	2	5	1	3	1	4	4
Asymmetric arm swing while running	2	2	1	3	3	3	5	4	1	3	2	2	5	1	3	1	4	2
Contralateral mirror movement	3	2	1	3	2	2	5	4	1	2	2	2	2	1	2	1	2	2
Reduced tremor	1	2	1	3	2	1	3	2	1	2	2	2	2	1	1	1	1	2
Micrography	4	2	3	3	3	2	4	5	4	x	4	2	2	5	3	1	4	4

PD4

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	Yes	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes
	Acceleration of pace	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	Reduced amplitude	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Number arrests in ongoing movement	0	0	2	2	0	0	0	0	2	2	0	0	0	0	2	0	5	1
2. Tandem gait performance	Normal tandem gait test?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	Yes	No	No	No	No	Yes	No	Yes	x	Yes	No	No	No	No	No	No	Yes	No
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Near identical lack of arm swing while walking and running?	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes	No	Yes	No	Yes	No
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No
6. Reduced tremor	During UPDRS 23,24,25,26	No	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No
7. Writing	Micrography	No	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
	Unstable writing pattern	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
8. Diagnosis	Abnormal DAT-SPECT?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A
	PD OR Atypical parkinsonism?	PD	AP	AP	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	PD	x
9. Contribution of the items to your conclusion above	Progressive deceleration	3	2	1	5	4	4	5	5	1	3	5	4	2	5	5	5	3	4
	Reduced amplitude	2	2	1	5	3	4	5	5	5	3	2	4	4	5	4	5	4	4
	Number of stops during video	1	2	4	1	2	1	1	3	3	2	2	x	2	2	2	1	3	4

Tandem gait performance	2	1	1	1	2	x	5	1	3	2	2	4	2	2	4	1	3	2
Re-emerging phenomenon	4	2	4	1	2	1	5	4	1	3	2	x	2	2	1	1	2	2
Asymmetric arm swing while walking	5	5	4	5	4	5	5	5	5	4	5	x	4	5	4	3	4	4
Asymmetric arm swing while running	3	4	5	5	2	4	5	4	5	2	4	x	4	2	4	2	4	2
Contralateral mirror movement	1	1	1	1	2	4	5	4	1	2	2	x	2	1	1	1	2	2
Reduced tremor	1	1	3	1	3	2	3	x	1	2	2	x	2	2	2	1	3	2
Micrography	2	1	4	1	2	1	1	4	1	3	2	x	3	2	4	1	2	4

PD5

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	Yes	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
	Acceleration of pace	No	No	Yes	No	No	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	Yes
	Reduced amplitude	No	No	Yes	No	No	No	Yes	No	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
	Number arrests in ongoing movement	0	0	0	0	0	x	0	0	2	0	0	0	0	0	~6	0	2	0
2. Tandem gait performance	Normal tandem gait test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	No	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	Yes	No	Yes	No	No	No	Yes	No	Yes	No	No	No	No	Yes	No	Yes	Yes	No
	Near identical lack of arm swing while walking and running?	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No	No
6. Reduced tremor	During UPDRS 23,24,25,26	n/a	N/A	N/A	N/A	N/A	No	n/a	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7. Writing	Micrography	No	No	Yes	No	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
	Unstable writing pattern	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No
8. Diagnosis	Abnormal DAT-SPECT?	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	N/A
	PD OR Atypical parkinsonism?	x	AP	PD	x	x	x	PD	x	PD	AP	x	x	x	PD	AP	PD	AP	x
9. Contribution of the items to your conclusion above	Progressive deceleration	2	2	4	5	3	5	5	5	5	4	4	3	4	3	3	4	3	4
	Reduced amplitude	4	2	3	5	3	5	5	5	2	4	4	3	4	3	3	4	3	4
	Number of stops during video	3	2	1	1	2	3	1	3	3	1	4	1	4	2	3	1	3	3

Tandem gait performance	3	1	5	1	2	1	5	1	4	3	4	2	2	5	2	1	4	2
Re-emerging phenomenon	4	1	1	1	2	1	5	4	1	1	4	1	2	2	1	1	2	4
Asymmetric arm swing while walking	3	3	5	1	4	5	5	5	5	4	4	3	5	5	3	3	4	4
Asymmetric arm swing while running	3	3	5	1	2	5	5	4	5	1	4	3	5	2	3	2	4	2
Contralateral mirror movement	4	1	1	1	2	4	5	4	3	4	4	2	3	2	3	1	2	3
Reduced tremor	2	1	1	1	3	1	3	2	1	1	4	4	2	2	1	1	2	2
Micrography	4	1	4	1	3	3	4	5	3	2	4	4	3	4	4	1	2	4

PD6

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes
	Acceleration of pace	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No
	Reduced amplitude	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Number arrests in ongoing movement	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	2
2. Tandem gait performance	Normal tandem gait test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	No	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	N/A
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Near identical lack of arm swing while walking and running?	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	No	No	No	No	No	No	nNo	No	No	No	No	No	No	No	No	No	No	No
6. Reduced tremor	During UPDRS 23,24,25,26	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7. Writing	Micrography	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	x	No	No
	Unstable writing pattern	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	x	Yes	No
8. Diagnosis	Abnormal DAT-SPECT?	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	N/A
	PD OR Atypical parkinsonism?	PD	AP	PD	x	x	PD	PD	PD	PD	AP	AP	PD	PD	x	PD	PD	PD	x
9. Contribution of the items to your conclusion above	Progressive deceleration	4	2	3	5	2	4	5	5	3	4	2	2	4	5	5	5	5	4
	Reduced amplitude	4	5	4	5	3	5	5	5	4	5	5	4	4	4	3	5	5	4
	Number of stops during video	2	1	1	1	2	3	3	3	1	2	2	2	2	3	1	x	3	3

Tandem gait performance	2	1	5	1	2	1	5	1	4	4	2	2	2	4	4	1	3	2
Re-emerging phenomenon	2	1	1	1	2	1	5	4	1	2	2	1	1	2	1	1	2	4
Asymmetric arm swing while walking	4	5	5	5	4	5	5	5	5	5	4	4	4	5	4	3	4	3
Asymmetric arm swing while running	4	3	5	5	3	5	5	4	5	1	4	3	4	3	4	2	4	2
Contralateral mirror movement	2	1	1	1	2	1	5	4	1	1	2	1	2	2	1	1	2	2
Reduced tremor	2	1	1	5	2	1	3	2	1	1	2	1	2	1	1	1	2	2
Micrography	1	1	1	1	3	1	4	5	1	1	2	1	2	5	1	1	2	4

PD7

		NT1	NT2	NT3	NT4	NT5	NT6	GN1	GN2	GN3	GN4	GN5	GN6	MD1	MD2	MD3	MD4	MD5	MD6
1. Bradykinesia	Deceleration of pace	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Acceleration of pace	No	No	Yes	No	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No
	Reduced amplitude	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Number arrests in ongoing movement	0	0	0	2	2	5	0	2	2	2	0	3	4	4	0	6	11	10
2. Tandem gait performance	Normal tandem gait test?	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	No
3. Re-emerging phenomenon	Re-emerging phenomenon during UPDR 20+21	Yes	No	No	Yes	No	Yes	Yes	No	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes
4. Asymmetric arm swing	Asymmetric Arm swing UPDRS 29	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Near identical lack of arm swing while walking and running?	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No
5. Contralateral mirror movement	Contralat. mirror movements UPDRS 23, 24, 25, 26?	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No
6. Reduced tremor	During UPDRS 23,24,25,26	No	No	No	No	No	No	No	N/A	No	No	No	No	No	Yes	No	No	Yes	No
7. Writing	Micrography	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
	Unstable writing pattern	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No
8. Diagnosis	Abnormal DAT-SPECT?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A
	PD OR Atypical parkinsonism?	PD	PD	AP	AP	PD	AP	PD	PD	PD	PD	PD	PD	PD	PD	AP	PD	AP	
9. Contribution of the items to your conclusion above	Progressive deceleration	4	3	3	5	4	5	5	5	5	4	2	4	5	5	5	5	4	N/A
	Reduced amplitude	4	5	4	5	4	4	5	5	5	4	4	4	5	5	4	5	4	N/A
	Number of stops during video	2	1	1	1	3	2	3	3	4	2	2	4	3	5	3	4	4	N/A

Tandem gait performance	3	3	5	5	3	4	5	1	3	2	4	3	3	4	5	1	4	N/A
Re-emerging phenomenon	4	1	1	5	2	3	5	4	1	3	2	4	2	5	1	2	2	N/A
Asymmetric arm swing while walking	4	4	5	1	4	4	5	5	4	4	5	4	3	5	3	3	4	N/A
Asymmetric arm swing while running	2	3	5	1	3	4	5	4	4	3	4	4	3	3	3	1	4	N/A
Contralateral mirror movement	4	1	1	1	2	2	5	4	3	2	2	4	3	1	4	1	2	N/A
Reduced tremor	2	1	1	1	2	1	3	2	1	3	2	3	2	3	1	1	3	N/A
Micrography	3	2	1	1	2	1	4	5	1	2	2	2	2	2	1	1	2	N/A

List of abbreviations

SWEDD Scans without evidence of dopamine deficit
PD Parkinson's disease
AP Atypical parkinsonism
NT Neurologist in training
GN General neurologist
MD Movement disorder expert

Chapter 7

Summary and discussion

The main question of this thesis is if the clinical diagnosis of neurodegenerative Parkinsonism and specifically PD can be improved by enhancing the clinical recognition of patients with a non-neurodegenerative form of Parkinsonism. These patients have a normal dopamine transporter (DAT) single-photon emission computed tomography (SPECT) scan (*i.e.*, scans without evidence of dopaminergic deficit (SWEDD)). The short answer is no, but there is good news.

The capabilities of DAT SPECT imaging

In chapter 2, we showed that DAT SPECT imaging is a highly reliable molecular imaging tool to determine whether there is nigrostriatal dopaminergic cell loss ante-mortem. In other words, if a physician has doubts if a patient has a neurodegenerative form of Parkinsonism or a non-neurodegenerative form of Parkinsonism, DAT SPECT imaging can eliminate those uncertainties. DAT SPECT imaging has a sensitivity and specificity of 98% to detect or exclude loss of striatal DAT binding in patients with clinically uncertain Parkinsonism. In studies that included patients with a diagnosis of PD in whom there was no clinical uncertainty 100% of the patients had an abnormal DAT SPECT.

In recent years, we and others commonly used non-selective SPECT tracers, such as [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)nortropane [^{123}I]FP-CIT or [^{123}I]β-carboxymethyoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT) to image the DAT. Although it has been shown that striatal binding of these tracers predominantly reflects binding to the DAT, these radiotracers cannot be used to assess extrastriatal DAT binding adequately.[1,2] In the past years, however, highly selective DAT tracers like [^{18}F]FE-PE2I for positron emission tomography (PET) have become available for clinical practice. The initial studies showed that [^{18}F]FE-PE2I PET has a discriminative power of at least 90% in detecting nigrostriatal cell loss.[3] The question remained if this highly DAT selective tracer would perform better in detecting nigrostriatal cell loss compared to the less selective DAT tracers [^{123}I]FP-CIT and [^{123}I]β-CIT. Recently, a direct comparison study between [^{123}I]FP-CIT SPECT and [^{18}F]FE-PE2I PET was performed which suggested that both techniques are highly reliable in detecting nigrostriatal cell loss with similar diagnostic properties.[4] However, this was a small study comparing 22 parkinsonian patients and 28 healthy controls. Considering that the diagnostic accuracy of [^{123}I]FP-CIT SPECT, to detect

or exclude nigrostriatal cell loss in PD, is already very high, it is unlikely that the selective DAT PET tracer will outperform [^{123}I]FP-CIT SPECT in detecting nigrostriatal cell loss.
Also, DAT SPECT imaging with [^{123}I]FP-CIT remains the most feasible method in detecting nigrostriatal cell loss in routine clinical practice, because PET is more expensive, less widespread available and currently sufficient experience in assessing these images is almost exclusively available in tertiary referral hospitals. Nevertheless, there are potential practical advantages of this PET tracer, such as the shorter interval between administration of the tracer and scanning – approximately one hour compared to three hours for [^{123}I]FP-CIT SPECT imaging – and the shorter acquisition time due to the higher efficiency of PET imaging.[5]

Although DAT SPECT imaging is highly reliable in detecting nigrostriatal cell loss in routine clinical practice, physicians are often also interested if the patient has PD or another neurodegenerative Parkinsonian disorder; *e.g.*, multiple system atrophy (MSA, particularly the parkinsonian variant MSA-P) or progressive supranuclear palsy (PSP). DAT SPECT imaging is unable to reliably discriminate between these various neurodegenerative diseases. The main reason is the considerable overlap in striatal DAT availability between PD, PSP and MSA-P on an individual level.[6]

However, with DAT PET imaging it may be possible to discriminate between these neurodegenerative disorders. By using [^{18}F]N-3-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)-nortropane ([^{18}F]FP-CIT) PET it was shown that the sensitivity and specificity for differentiating PSP from PD were 94% and 92%, respectively. For the distinction of MSA from PD, sensitivity and specificity were 90% and 45%.[7] The higher efficiency and spatial resolution of DAT PET offer the possibility to adequately discriminate radiotracer binding in smaller subdivisions of the striatum as compared to DAT SPECT studies, which may result in a better discriminative power between PD and atypical parkinsonian syndromes; *i.e.*, MSA-P or PSP versus PD. Although to date, no study has been published that investigated this clinical dilemma with the novel selective DAT PET tracer [^{18}F]FE-PE2I, it is likely that this tracer will have similar test characteristics as [^{18}F]FP-CIT PET. If the aforementioned aspects of costs and availability are improved, DAT imaging with PET

might become a superior technique for use in clinical practice considering the reliable discrimination between the different forms of neurodegenerative Parkinsonism.

The use and assessment of DAT SPECT imaging in the Netherlands

In chapter 3 we showed that 10.5% of the Dutch neurologists never use DAT SPECT imaging in clinical practice and 15.7% of the neurologists expect to get additional information from the scan. The latter group anticipates that the DAT SPECT also discriminates between the different forms of neurodegenerative Parkinsonism; *e.g.*, PD versus MSA. As discussed earlier, asymmetrical putamen DAT availability is more typical for PD compared to the other forms of neurodegenerative parkinsonian disorders at a group level, but DAT SPECT imaging does not help to differentiate between the neurodegenerative parkinsonian disorders at an individual level.[6] The results of our survey demonstrate that there is room for improvement regarding the use of this diagnostic tool in clinical practice. This could be easily achieved through enhancing the critical appraisal by nuclear medicine physicians of the DAT SPECT imaging requests and providing feedback to the referring physician, and/or by educating neurologists and other physicians requesting DAT SPECT imaging on the capabilities and limitations of this technique.

Furthermore, we demonstrated that the visual assessment of [^{123}I]FP-CIT SPECT imaging in routine clinical practice by nuclear medicine physicians and radiologists is highly reliable. The interrater agreement was 98% between general radiologists/nuclear medicine physicians and an expert in DAT imaging. This is in contrast to previous studies stating that visual assessments should be performed by experienced observers and/or improves the reader confidence in the interpretation of the DAT SPECT images.[8-10] It was previously debated that there is considerable interobserver variability in region-of-interest (ROI) selection and therefore more false positive/false negative results if the assessment is performed by less experienced observers.[11] We think that the widespread use of DAT SPECT imaging in the Netherlands combined with a small number of centers that train physicians in becoming nuclear medicine specialists helps to increase the interobserver reliability since most of the (physicians in these) centers have extensive experience in assessing DAT SPECT images.

Dyskinesias and DAT SPECT imaging in PD

After five years of levodopa treatment, approximately 30-40% of patients suffer from levodopa-induced dyskinesia (LID), increasing to 40-60% after 10 years of treatment.[12,13] The pathophysiology of dyskinesia is largely unknown. One theory consists of the involvement of serotonin neurons. The theory behind the possible involvement of serotonin neurons is that there is a relatively mild loss of serotonin neurons compared to the loss of dopamine neurons in PD patients with LID. In patients with LID there is less loss of serotonin neurons.[14,15] The serotonergic neurons in the striatum can also take up, store, and release dopamine, but these neurons lack the auto-regulatory feedback mechanisms of dopaminergic neurons to release dopamine adequately (serotonergic neurons lack dopamine D_2 auto-receptors and the DAT).[16,17] As a result of the lack of these mechanisms, dopamine release from serotonin nerve terminals in PD may be poorly regulated, resulting in uncontrolled excessive swings in dopamine release and consequently the appearance of dyskinesias.

In chapter 4, we reported that we found no correlation between extrastriatal midbrain serotonin transporter (SERT), striatal (*i.e.*, caudate nucleus, putamen, and whole striatum) DAT and SERT-to-DAT ratios, and the onset of dyskinesias using [^{123}I]β-CIT SPECT imaging in patients with PD.

In the last couple of years, selective SERT tracers for PET have become available. With these tracers it is possible to measure intrastriatal SERT. In several studies, using [^{123}I]FP-CIT SPECT to assess striatal DAT binding and the SERT tracer [^{11}C]DASB to assess striatal SERT binding, a positive correlation between LID and SERT-to-DAT binding ratio was found.[18,19] This finding supports the involvement of serotonergic neurons in the development of LID. Interestingly, three PD patients who underwent an intrastriatal transplantation of fetal ventral mesencephalic tissue developed severe dyskinesias in the years post-transplantation.[19,20] In these patients the ratio of serotonergic to dopaminergic innervation in the grafted putamen, as estimated by the use of a selective SERT tracer ([^{11}C]DASB) and the PET tracer [^{18}F]FDOPA, was significantly increased in all patients. Remarkably, the inhibition of serotonin neuron activity by systemic administration of a 5-HT_{1A} agonist, which decreases the activity of serotonergic neurons, suppressed these dyskinesias.

The fact that we did not find a correlation between LID and extrastriatal midbrain SERT binding, striatal (caudate nucleus, putamen, whole striatum) DAT and SERT-to-DAT ratios may be caused by the use of a non-selective DAT/SERT tracer which prevented the opportunity to measure SERT expression within the striatum. In order to assess if the abovementioned theory is correct, a study with long-term follow-up of PD patients should be performed with selective SERT and, possibly selective DAT tracers, at baseline (prior to dopaminergic therapy), to assess striatal SERT-to-DAT binding ratios.

Early SPECT imaging and definitive clinical diagnosis

Differentiating PD from other neurodegenerative forms of Parkinsonism like MSA-P can be challenging especially early in the course of the disease. In the early stages of the various neurodegenerative diseases many signs and symptoms overlap.[21,22] The more distinctive features generally develop later in the course of the disease. Diseases like MSA-P and PSP, however, have a considerable worse prognosis compared to PD. Therefore, early identification of the exact diagnosis is desirable so that the patient knows what to expect. This differentiation will become even more essential if disease-modifying therapies become available.

In chapter 5 we demonstrated that by using DAT SPECT imaging, specifically [^{123}I]β-CIT SPECT, there was no correlation between striatal DAT (caudate nucleus, putamen, whole striatum), midbrain SERT and SERT-to-DAT ratios and the final clinical diagnosis after long-term follow-up. It was previously shown that midbrain SERT availability in patients suffering from MSA was significantly reduced compared to patients with PD.[23,24] The patients in these studies were established clinical cases with a mean disease duration of 24 months. However, in our study imaging was performed at an early-stage (mean disease duration 0.2 years for MSA and 1.2 years for PD patients) and we did not find significant differences in striatal DAT, midbrain SERT and SERT-to-DAT ratios and the respective diagnosis. Therefore we concluded that non-selective tracers like [^{123}I]β-CIT cannot provide a reliable discrimination between PD and other neurodegenerative forms of Parkinsonism at an early stage based on the striatal DAT, midbrain SERT and SERT-to-DAT ratios.

However, using [^{18}F]FP-CIT PET it was demonstrated that patients with PSP and MSA showed more prominent and earlier DAT loss compared to PD.[6] If our study was repeated using [^{18}F]FP-CIT PET (or [^{18}F]FE-PE2I) there could be a correlation and it might be possible to differentiate between these disorders at an early-stage.

Outside the scope of this thesis, but important to mention, is that there have been very promising results in the field of disease-specific patterns of regional glucose metabolism with the use of PET imaging (for example [^{18}F]FDG). Cerebral [^{18}F]FDG PET imaging could also allow for accurate differentiation between the various forms of neurodegenerative Parkinsonism.[25]

Identifying patients with SWEDD

Patients with SWEDD represent a clinical misdiagnosis of PD. These patients have a clinical diagnosis of PD but normal DAT SPECT imaging. Follow-up studies showed that the vast majority of these patients do not suffer from a neurodegenerative form of Parkinsonism.[26-29]

However, these SWEDD patients cannot reliably be identified clinically by movement disorders experts, general neurologists and/or neurologists in training among a group of patients with a clinical diagnosis of PD and abnormal DAT SPECT imaging based on a video assessment, as we showed in chapter 6. Recent literature demonstrated that imaging of the nigrostriatal dopaminergic pathway seems to be the only validated technique to aid the differential diagnosis between neurodegenerative Parkinsonism and non-neurodegenerative Parkinsonism.[30]

Unfortunately, due to the small number of patients with confirmed SWEDD (N=3) in the LEAP trial, we were unable to assess if specific selected clinical features could help in the clinical identification of patients with SWEDD. The small number of patients with SWEDD could possibly be explained by a tendency of neurologists to refer only patients in whom they felt sure about the diagnosis. If there was clinical doubt, patients were not referred for inclusion, or DAT SPECT imaging was performed before referral for the LEAP trial. This is supported by the fact that a large number of patients (n=105) underwent DAT SPECT imaging as part of routine clinical practice (prior to referral for the LEAP-clinical trial).

I would recommend, in in future clinical trials that use DAT SPECT or PET imaging, to record a comprehensive neurological examination on video to reassess the clinical diagnosis at diagnosis in light of normal DAT imaging results. This might be an important way to improve the accuracy of identification of patients with non-neurodegenerative Parkinsonism based on clinical features.

Final remarks

Based on the research in this thesis, I advise all physicians that see patients with the suspicion of PD to perform DAT SPECT imaging when there is clinical doubt if the patient has a neurodegenerative form of Parkinsonism or non-neurodegenerative Parkinsonism. If there is clinical doubt between different forms of neurodegenerative Parkinsonism DAT SPECT imaging is not helpful. As mentioned earlier, [^{18}F]FDG PET and possibly PET imaging with selective DAT tracers might be able to reliably do so. Unfortunately, this technique, and most importantly the specific needed experience in assessing these images, is not widespread available yet and not yet validated to perform this test adequately.

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Chapter 8

Nederlandse samenvatting

De ziekte van Parkinson is een diagnose die door veel neurologen in de spreekkamer kan worden gesteld op basis van symptomen en klinische verschijnselen. Het is bekend dat 24-35% van de patiënten waarbij initieel de diagnose ziekte van Parkinson is gesteld uiteindelijk een andere diagnose krijgen. In circa één derde van deze patiënten (4.7-14.7% van totaal) is geen sprake van een zogenoemde progressieve neurodegeneratieve aandoening gekenmerkt door verlies van dopamine-producerende neuronen (nigrostriatale degeneratie). Deze patiënten hebben dus de diagnose ziekte van Parkinson gekregen maar op een dopamine transporter scan (DAT SPECT) zijn geen afwijkingen. Dit wordt in de literatuur ook wel SWEDD (scans without evidence of dopaminergic deficit) genoemd. Patiënten die zich bij de neuroloog melden, en waarbij parkinsonachtige verschijnselen worden vastgesteld (Parkinsonisme) kunnen worden ingedeeld in twee groepen; neurodegeneratief parkinsonisme en non-neurodegeneratief parkinsonisme. De hoofdvraag van dit proefschrift is of de klinische diagnose kan worden verbeterd om dit onderscheid beter te kunnen maken in de spreekkamer.

In **hoofdstuk 2** hebben we middels een systematische review van de literatuur laten zien dat de DAT SPECT scan een uiterst betrouwbaar instrument is om bij patiënten met beginnend parkinsonisme vast te stellen of sprake is van nigrostriatale degeneratie. De sensitiviteit en specificiteit van de DAT SPECT scan is 98% bij patiënten waarbij de neuroloog twijfel heeft of de patiënt parkinsonisme heeft door nigrostriatale degeneratie of niet. Bij patiënten waarbij er geen klinische twijfel is loopt de sensitiviteit op tot 100%. Ondanks dat dit een zeer betrouwbaar instrument is blijkt dat 10.5% van de Nederlandse neurologen nooit gebruik maken van de DAT SPECT scan (**hoofdstuk 3**) en dat 15.7% meer informatie verwacht te krijgen van de DAT SPECT scan dan mogelijk is; namelijk onderscheid tussen verschillende vormen van neurodegeneratief parkinsonisme (o.a. ziekte van Parkinson, multipele systeem atrofie, progressieve supranucleaire paralyse). Deze gegevens laten zien dat er ruimte is voor verbetering aangaande de inzet van DAT SPECT. Daarnaast hebben we aangetoond dat visuele beoordeling door nucleair geneeskundigen en radiologen in de dagelijkse Nederlandse praktijk betrouwbaar is. De interobserver betrouwbaarheid tussen experts op het gebied van DAT SPECT scans en nucleair geneeskundigen/radiologen was 98%. Eerder werd aangenomen dat voor een betrouwbare visuele beoordeling van DAT SPECT scans uitgebreide ervaring nodig is.

In **hoofdstuk 4** hebben we gekeken of het mogelijk was om, op basis van serotonine transporter, DAT en de serotonine transporter-DAT ratio's gemeten met [^{123}I]β-CIT SPECT scans, te voorspellen welke patiënten met de ziekte van Parkinson het grootste risico hadden op het ontwikkelen van onwillekeurige bewegingen (dyskinesieën) later in het ziekteproces. Helaas bleek dit, met de gebruikte tracer ([^{123}I]β-CIT) niet mogelijk. Er werd in overeenstemming met de literatuur wel gevonden dat het risico op het ontwikkelen van dyskinesieën gecorreleerd is met de leeftijd waarop de parkinson klachten begonnen. Patiënten bij wie op jongere leeftijd de diagnose wordt gesteld hebben een hoger risico op het ontwikkelen van dyskinesieën.

In **hoofdstuk 5** hebben we laten zien dat er geen relatie was tussen de beschikbaarheid van serotonine transporter (SERT) en SERT-DAT ratio's en de uiteindelijke diagnose na langdurige klinische follow-up.

In **hoofdstuk 6** beschrijven we dat het voor gerenommeerde bewegingsstoornissen experts, algemeen neurologen en neurologen in opleiding niet mogelijk was om patiënten met een SWEDD te onderscheiden van patiënten met een afwijkende DAT SPECT scan. Om dit onderscheid te maken, kregen ze beschikking over een uitgebreid neurologisch onderzoek dat op video was vastgelegd. Onze bevinding dat patiënten met parkinsonisme met een normale DAT SPECT niet goed te onderscheiden zijn van patiënten met een afwijkende DAT SPECT scan, wordt ondersteund door recent gepubliceerde literatuur, waarin tevens wordt geconcludeerd dat dit onderscheid alleen betrouwbaar gemaakt kan worden door beeldvorming van het nigrostriatale systeem. Door een onverwacht klein aantal patiënten met SWEDD in onze studie was het helaas niet mogelijk om per item van het neurologisch onderzoek te bestuderen of dit mogelijk zou kunnen bijdragen aan de identificatie van patiënten met SWEDD. Hierbij zou ik er daarom voor willen pleiten dat bij toekomstige klinische studies bij de ziekte van Parkinson, waarbij gebruik gemaakt wordt van DAT SPECT of positron emission tomography (PET) scans, er tevens een uitgebreid neurologisch onderzoek op video wordt vastgelegd. Op deze manier, mogelijke de enige manier, is het mogelijk om systematisch te evalueren of er klinische kenmerken zijn van patiënten met SWEDD die kunnen helpen om in de toekomst wel het onderscheid te maken tussen beide groepen in de spreekkamer.

Op basis van het onderzoek in dit proefschrift adviseer ik alle collega's die patiënten zien met de verdenking op de ziekte van Parkinson waarbij twijfel is of sprake is van de ziekte van Parkinson om een DAT SPECT te verrichten om het onderscheid te maken tussen neurodegeneratief parkinsonisme en non-neurodegeneratief parkinsonisme. Hoewel het ook zeer informatief kan zijn om onderscheid te maken tussen de verschillende oorzaken van neurodegeneratief parkinsonisme is dit, op dit moment, helaas nog niet mogelijk in de klinische praktijk met nucleaire scans. Recente studies hebben laten zien dat dit wellicht wel mogelijk is met het gebruik van o.a. [^{18}F]FDG PET. Helaas is deze techniek, en nog belangrijker de specifieke expertise die nodig is om deze scans te beoordelen, op dit moment nog beperkt beschikbaar.

Contributing authors

Current affiliations of contributing authors in alphabetical order

Henk W. Berendse

Department of Neurology, Amsterdam University Medical Centers, Vrije Universiteit, de Boelelaan 1117, Amsterdam, The Netherlands

Rob M.A. de Bie

Department of Neurology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

Caroline J. van Boheemen

Department of Neurology, Saint Anna hospital, Geldrop, The Netherlands

Jan Booij

Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

Joke M. Dijk

Department of Neurology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

Carsten Eggers

Department of Neurology, University Medical Center Gießen und Marburg, Marburg, Germany

Alberto Espay

James J. and Joan A. Gardner Family Center for Parkinson's disease and Movement Disorders, University of Cincinnati, Cincinnati, Ohio, USA

Susan Fox

Edmond J. Safra Program in Parkinson's Disease and Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University of Toronto, Toronto, Canada

Rob J. de Haan

Clinical research unit, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

Anthony E. Lang

Edmond J. Safra Program in Parkinson's Disease and Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University of Toronto, Toronto, Canada

Hamdia Samin

Department of Neurology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

Mike Samuel

Department of Neurology, King's College Hospital, London, United Kingdom

Monty Silverdale

Salford Royal NHS Foundation Trust, University of Manchester, Manchester, United Kingdom

Gerrit Tissingh

Department of Neurology, Zuyderland Medical Center, Heerlen, The Netherlands

Hein Verberne

Department of Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

Constant V.M. Verschuur

Department of Neurology, Albert Schweitzer hospital, Dordrecht, The Netherlands

Ania Winogrodzka

Department of Neurology, Noordwest clinics, Alkmaar, The Netherlands

Background information cover

The story of the Parkinson Tulip began in 1980 in the Netherlands when J.W.S. Van der Wereld, a Dutch horticulturalist, with Parkinson's disease (PD), developed a red and white tulip, which he named the 'Dr. James Parkinson' tulip, to honor Dr. James Parkinson.

The tulip received the Award of Merit in 1981 from the Royal Horticultural Society in London and also received the Trial Garden Award from the Royal General Bulb Growers of Holland.

On April 11, 2005, the Red Tulip was launched as the Worldwide Symbol of Parkinson's disease at the 9th World Parkinson's disease Day Conference in Luxembourg. Variations of the red tulip are now used by many Parkinson's disease organizations worldwide.

Dankwoord

Dit proefschrift had ik niet kunnen schrijven zonder de inzet en betrokkenheid van velen. Ik wil graag iedereen bedanken die een bijdrage heeft geleverd aan het onderzoek in dit proefschrift, een aantal mensen wil ik in het bijzonder bedanken.

Allereerst wil ik **alle patiënten en hun familieleden** die hebben deelgenomen aan de LEAP-studie bedanken. Zonder uw medewerking was dit proefschrift er niet gekomen.

Professor dr. R.M.A. de Bie, Beste Rob, sinds 2012 heb ik het grote genoegen gehad om mijn vaardigheden als onderzoeker maar vooral ook als clinicus te mogen ontwikkelen onder jouw vleugels. Ik bewonder jou om je scherpe klinische blik en kritische houding ten aanzien van onderzoek. De komende tijd hoop ik nog veel van je te mogen leren.

Professor dr. J. Booij, Beste Jan, het was voor mij onverwacht dat een nucleair geneeskundige hotshot een van mijn promotoren zou worden. Ik ben je dankbaar voor de talloze uren die je me hebt geholpen bij het leren vervaardigen en interpreteren van de DAT SPECT scan. Jouw nuchterheid, rust en enthousiasme hebben me enorm geholpen bij het schrijven van dit proefschrift.

De overige leden van mijn promotiecommissie: **prof. dr. van den Berg, prof. dr. Diercx, dr. Dijk, dr. van de Giessen, prof. dr. van Hilten, prof. dr. Roos.** Dank dat jullie zitting hebben genomen in mijn commissie en dank voor de tijd die jullie hebben gestoken in het beoordelen van mijn proefschrift. Beste **Yvo** jou wil ik in het bijzonder bedanken voor de belangrijke bijdrage aan mijn vorming tot neuroloog.

Alle mede auteurs. Bedankt voor jullie kritische blik en samenwerking.

De onderzoeksverpleegkundigen van de LEAP-studie **Stefanie de Vries, Sonja Cuppen, Janneke Prudon, Danny van der Sluis, Lars Oude Nijhuis, Jorine van Heeden, Tiny Simon en Jolan Hendriks.** Dank voor al het harde werk aan de LEAP-studie, zonder jullie was de LEAP-studie nooit een succes geworden.

Mijn (ex-)kamergenoten, **Daan Velseboer, Constant Verschuur, Henrieke Frequin en Laura van Meenen.** Dank voor alle gezelligheid en afleiding tijdens mijn promotie.

Vincent Odekerken. Vinnie, van kamergenoot, tot supervisor tot opleider. Jouw loopbaan is minstens zo bijzonder als de manier waarop je invulling geeft aan deze rollen. Ik ben je erg dankbaar voor je humor, kennis en ook de steun tijdens mindere momenten.

Jelwin Stam en Timo ten Brinke. Dank dat jullie mijn paranimfen willen zijn. **Jelwin**, we kennen elkaar inmiddels meer dan 20 jaar en ondanks het feit dat we elkaar door drukte soms minder vaak spreken dan ons lief is, is het altijd goed als we elkaar weer zien. Ik kan me geen betere vriend voorstellen.
Timo, jouw streken halen het beste en het slechtste in me naar boven en ik ben erg blij met alle bijzondere momenten die we hebben gedeeld. Van zeuren over het onderzoek tot de lol van meten van de loopsnelheid van onze collega's voor het kerstnummer van de BMJ.

Jeroen Blom. Beste sensei, Je bent op een belangrijk moment in mijn leven gekomen en wil je bedanken voor alle no-nonsense adviezen en eindeloze geduld op de mat. Ik heb ongelooflijk veel plezier om in jouw dojo te mogen trainen. Osu!

Mijn ouders, lieve pap en mam bedankt voor de onvoorwaardelijke steun en liefde die ik van jullie heb gekregen. We hebben als gezin veel mooie momenten maar helaas ook veel minder leuke momenten meegemaakt. Mam, wat ben ik ongelooflijk gelukkig dat jij dit moment nog mag meemaken.

Mijn schoonouders, lieve Jos en Marry, Wat heb ik het toch getroffen met jullie als schoonouders. Ik wil jullie bedanken voor de talloze momenten dat jullie zijn ingesprongen en de manier waarop ik onderdeel mag uitmaken van jullie familie.

Lieve **Martine,** ik heb eerlijk gezegd geen idee hoe ik jou zou kunnen bedanken voor alle steun, ruimte en vooral liefde de je me hebt gegeven. Je bent een voorbeeld van een goed mens en fantastische moeder. Ik kijk uit naar alle jaren die ik samen met je door mag brengen. You raise me up.

Lieve **Noah, Joshua en Manuel.** Mijn kerels, ik ben zo blij met jullie in mijn leven. Jullie hebben er voor gezorgd dat ik begrijp wat er echt belangrijk is in het leven. Ik kan niet wachten om nog veel meer herinneringen met jullie te maken.

Curriculum Vitae

Personal information

Name	Suwijn, Sven Roman
Nationality	Dutch
Date of Birth	12 December 1985

Education and training

2015-present	**Neurologist in training** Amsterdam University Medical Centers
2014	**Resident Neurology** Zaans Medical Center
2012-present	**PhD student** Amsterdam University Medical Centers
May-Dec 2011	**Resident Neurology** Northwest Clinics, Alkmaar
Jan-May 2011	**Resident Neurosurgery** Radboud University Medical Center
Nov 2010-Jan 2011	**Resident Neurology** Northwest Clinics, Alkmaar
2004-2010	**Medical School** University of Amsterdam – Academic Medical Center

1998-2004	**Voorbereidend wetenschappelijk onderwijs** Gemeentelijke scholengemeenschap, Schagen

Organisational skills

2016-2017	AIOS+ traject Noordwest ziekenhuisgroep (medisch management)
2016-2017	Lid VIM commissie Neurologie, Northwest clinics, Alkmaar
2014	Lid VIM commissie Neurologie Zaans Medisch Centrum
2011	Lid Werkgroep prospectieve risico inventarisatie rondom de opgenomen patiënt met diabetes, Medisch Centrum Alkmaar
2010	Lid Werkgroep antistolling en chirurgie, Northwest clinics, Alkmaar

Publications

1	Scapula alata na neurotrauma [Article in Dutch] Suwijn SR, Kurt E, Haitink CM Medisch Contact. 2010;47:2541
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Graduate School portfolio

	Year	ECTS
General courses		
- BROK - NFU/ UvA, Amsterdam	2012	1.5
- Re-registration BROK	2016	0.2
- Practical biostatistics	2013	1.1
- Clinical Epidemiology	2013	0.6
- Basiscursus medisch management	2016	
Seminars, workshops and lectures		
- Workshop Parkinson's disease, Bilderberg hotel, Amsterdam	2012	0.1
- Werkgroep bewegingsstoornissen, Figi Hotel Zeist	2013	0.1
- Nascholingsavond, ziekte van Parkinson, Van der Valk Hotel, Maastricht	2013	0.1
- Clinical seminars at Amsterdamsche Neurologen Vereeniging (6 per year)	2012-2020	2.0
- Clinical seminars Neurology, Academic Medical Centre (40 per year)	2012-2020	8.6
- Masterclass Bewegingsstoornissen, Schoorl	2018	1.0

Presentations and Posters		
- Poster at MDS Congress Dublin	2012	0.5
- Poster at scientific meeting Nederlandse vereniging voor neurologie	2012	0.5
- Poster at MDS Congress Sydney	2013	0.5
- Poster at scientific meeting Sint Lucas Andreas hospital, Amsterdam	2012-2013	0.5
- LEAP(-DAS)-study presentations (40x)	2012-2013	0.5
- Poster at World Parkinson day, Eindhoven	2013	0.5
- Presentation at Amsterdamsche Neurologen Vereeniging	2016	0.5
- Poster presentation at scientific meeting Nederlandse vereniging voor neurologie	2019	0.5
- Poster at MDS Congress, Nice	2019	0.5
Scientific conference		
- MDS Congress, Dublin	2012	1.25
- Scientific meeting Nederlandse vereniging voor neurologie	2012	0.25
- MDS Congress, Nice	2019	1.25
- Scientific meeting Nederlandse vereniging voor neurologie	2019	0.25
Journal club		
- Journal club (1 per month)	2012-2015	2.0
- Movement disorders video session (40 per year)	2012-2015	4.0

	Year	ECTS
Lecturing		
- Neurological examination for interns	2012	0.5
- Neurological examination for interns (15x)	2013-2020	2
Tutoring, Mentoring		
- Guidance of bachelor thesis student	2016	1.0
- Guidance of bachelor thesis student	2018	1.0
Supervising		
- Survey neurological examination for medical students	2012-2013	0.5