Review Article

Nuclear Imaging in the Diagnosis of Clinically Uncertain Parkinsonian Syndromes

Ralph Buchert, Carsten Buhmann, Ivayla Apostolova, Philipp T. Meyer, Jürgen Gallinat

Department of Diagnostic and Interventional Radiology and Nuclear Medicine, University Medical Center Hamburg-Eppendorf: Dr. rer. nat. Ralph Buchert, PD Dr. med. Ivayla Apostolova

Department of Neurology, University Medical Center Hamburg-Eppendorf: Prof. Dr. med. Carsten Buhmann

Department of Nuclear Medicine, Medical Center—University of Freiburg: Prof. Dr. med. Dr. nat. med. Philipp T. Meyer

Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf: Prof. Dr. med. Jürgen Gallinat

Summary

Background: Parkinsonian syndromes are classified by etiology mainly on clinical grounds, that is, on the basis of the clinical manifestations and with the aid of conventional ancillary studies. In most cases, the clinical diagnosis is clear. In up to 30% of cases, however, the etiological classification remains uncertain after completion of the basic clinical diagnostic evaluation, and additional investigation with nuclear imaging may be indicated. In particular, cerebral single-photon emission computed tomography (SPECT) with dopamine transporter (DAT) ligands may be helpful. DAT-SPECT can be used to demonstrate or rule out nigrostriatal degeneration and thereby differentiate neurodegenerative parkinsonian syndromes from symptomatic parkinsonian syndromes and other differential diagnoses. Positron emission tomography (PET) with the glucose analogue [^{18}F]fluorodeoxyglucose (FDG) can be used to identify disease-specific patterns of neuronal dysfunction/degeneration in order to differentiate the various neurodegenerative parkinsonian syndromes from one another.

Methods: In this review, we summarize the current state of the evidence on DAT-SPECT and FDG-PET for the indications mentioned above on the basis of a selective review of the literature.

Results: DAT-SPECT has been adequately validated as an in vivo marker for nigrostriatal degeneration. Studies using the clinical diagnosis of a movement disorders specialist over the course of the disease as a reference have shown that DAT-SPECT is 78–100% sensitive (median, 93%) and 70–100% specific (median, 89%) for the differentiation of neurodegenerative parkinsonian syndromes from symptomatic parkinsonism and other differential diagnoses in clinically unclear cases. DAT-SPECT scanning led to a change of diagnosis in 27–56% of patients (median, 43%) and to a change of treatment in 33–72% (median, 43%). FDG-PET enables the differentiation of atypical neurodegenerative parkinsonian syndromes from the idiopathic parkinsonian syndrome (i.e., Parkinson's disease proper) with high sensitivity and specificity (both approximately 90%), when the clinical diagnosis by a movement disorders specialist over the course of the disease is used as a reference.

Conclusion: DAT-SPECT has been well documented to be highly diagnostically accurate and to have a relevant influence on the diagnosis and treatment of patients with clinically uncertain parkinsonian or tremor syndrome. It has not yet been shown to improve patient-relevant endpoints such as mortality, morbidity, and health-related quality of life; proof of this will probably have to await the introduction of neuroprotective treatments. The current evidence for the high differential diagnostic accuracy of FDG-PET in neurodegenerative parkinsonian syndromes needs to be reinforced by prospective studies with neuropathological verification of the diagnosis.

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The term "clinically uncertain parkinsonian syndrome" refers to symptom constellations with akinesia and at least one of the cardinal symptoms rigor, resting tremor, and postural instability (1). In addition to Parkinson's disease (idiopathic parkinsonian syndrome, IPS) (2), the causes of parkinsonian syndromes include the atypical neurogenerative parkinsonian syndromes (APS) such as multiple system atrophy (MSA) (3), progressive supranuclear palsy (PSP) (e1), and corticobasal syndrome (CBS)—the latter of which neuropathologically often results from corticobasal degeneration (CBD) (e2). These have to be distinguished from symptomatic parkinsonian syndromes and other differential diagnoses. Symptomatic parkinsonian syndromes can develop as a result of structural brain lesions (ischemic, traumatic, tumor-related), medication effects, intoxication, as well as inflammatory and metabolic disorders. Of great importance in clinical practice is vascular parkinsonian syndrome in subcortical arteriosclerotic encephalopathy. The differential diagnoses include normal pressure hydrocephalus, essential tremor, and (rarely) dopa-responsive dystonia. The different symptomatic

parkinsonian syndromes as well as the differential diagnoses require completely different therapeutic approaches, and early diagnosis is crucial. The early differential diagnosis of the neurodegenerative parkinsonian syndromes is also crucial for adequately patient-centered therapy. In IPS this means early medication treatment (e3) and, over the course of the illness, different pharmacological strategies in order to improve patients' quality of life (e4, e5). Patients with APS have a much poorer prognosis and derive little benefit (MSA, PSP-P) or no benefit at all (CBS and PSP-RS) from dopamine substitution treatment (e6). The correct etiological classification is therefore important in order to advise patients from a sociomedical perspective and spare them from undergoing unhelpful treatment that potentially causes adverse effects while initiating adequate symptomatic treatment measures (e6).

The etiological classification of parkinsonian syndromes is done primarily on a clinical basis—that is, on the basis of symptoms and by using conventional additional investigations, such as cranial magnetic resonance imaging (MRI) in order to rule out structural lesions (1). In the setting of non-specialist care, the clinical IPS diagnosis is accurate in about 75%, when made by a movement disorder specialist the diagnosis is accurate in 80% at the initial examination and in about 85% during follow-up examinations (4). The clinical APS diagnosis is less accurate (e7, e8). These numbers demonstrate the need for additional investigations for the purpose of etiological classification in cases that are clinically uncertain.

The guideline "Idiopathic Parkinsonian Syndrome" of the German Society of Neurology (DGN) and the Association of the Scientific Medical Societies in Germany (AWMF), which was updated in 2016, lists the following additional investigations:

- Cerebral single-photon emission computed tomography (SPECT) with tracers for the dopamine transporter (DAT) ("DAT-SPECT should be undertaken early on in the disease course to confirm nigrostriatal deficit in clinically uncertain parkinsonian or tremor syndromes") and
- Cerebral positron emission tomography (PET) with the glucose analogue [^{18}F]fluorodeoxyglucose (FDG) to detect neuronal dysfunction/degeneration ("FDG-PET can be used in selected cases for the best possible differential diagnostic classification of neurodegenerative parkinsonian syndromes, especially for the differentiation of atypical neurodegenerative parkinsonian syndromes from idiopathic parkinsonian syndrome") (1).

This review article summarizes studies of DAT-SPECT and FDG-PET for the indications mentioned in the guideline. We included recent publications ("recent" is taken to mean the time period since 2015—that is, after the literature selection for evaluating nuclear imaging in the DGN/AWMF guideline). DAT-SPECT will be discussed in greater detail here than FDG-PET because of the stronger guideline recommendation. For [^{123}I]metaiodobenzylguanidine scintigraphy of the noradrenergic innervation of the heart for the purpose of distinguishing MSA from IPS, the reader is referred to the pertinent review articles (5, e9).

DAT-SPECT in the diagnostic evaluation of parkinsonian syndromes

We conducted a literature search in PubMed, using the search term "ioflupane OR FP-CIT OR datscan OR DAT-scan OR β-CIT OR ([(dopamine transporter) OR DAT] AND [(single photon emission tomography) OR SPECT OR SPET])", which yielded 2476 hits on 17 June 2019. Furthermore, we undertook a backward search on the basis of selected publications and a forward search on Web of Science.

IPS and APS are accompanied by the loss of dopaminergic neurons in the substantia nigra and its nerve endings in the striatum (nigrostriatal degeneration) (e10–e13). Symptomatic parkinsonian syndromes and the differential diagnoses mentioned above are as a rule not accompanied by nigrostriatal degeneration.

Reduced DAT availability in the striatum is an appropriate marker for nigrostriatal degeneration in IPS since the degeneration of dopaminergic nerve endings in the striatum is very pronounced even at the early disease stages (e14–e16). Compensatory downregulation of the DAT expression in the remaining nerve endings results in more pronounced striatal DAT loss (e17–e19). To differentiate parkinsonian syndromes with relevant nigrostriatal degeneration (IPS and APS) from parkinsonian syndromes without relevant nigrostriatal degeneration (symptomatic parkinsonian syndromes, differential diagnoses) on the basis of the availability of striatal DAT, the DAT ligand N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[^{123}I] iodophenyl) nortropane ([^{123}I]ioflupane, [^{123}I]FP-CIT) has been licensed as a tracer for SPECT (6). No further DAT tracers for SPECT (e20–e24) have been licensed to date.

As an in-vivo marker of nigrostriatal degeneration, DAT-SPECT is well validated by comparisons with postmortem examinations in rodents (e25–e28), macaques (e29–e31), and patients (7–9).

In order to assess the results of DAT-SPECT, visual interpretation of the image (without quantitative evaluation) is usually sufficient (10). Agreement between different readers is usually good or very good (11, e32, e33). The proportion of borderline findings is below 10% (12, e34). The direct comparison of DAT-SPECT and DAT-PET to detect nigrostriatal degeneration at the symptomatic stage of neurodegenerative parkinsonian syndromes does not show any practice-relevant inferiority for DAT-SPECT compared with DAT-PET, although PET provides superior image quality with respect to spatial resolution and statistical noise (13, e35, e36). The explanation is that motor symptoms in IPS become obvious only from a DAT loss of at least 50% in the posterior putamen (14), and this large effect can be detected reliably by using DAT-SPECT too (*Figure 1*).

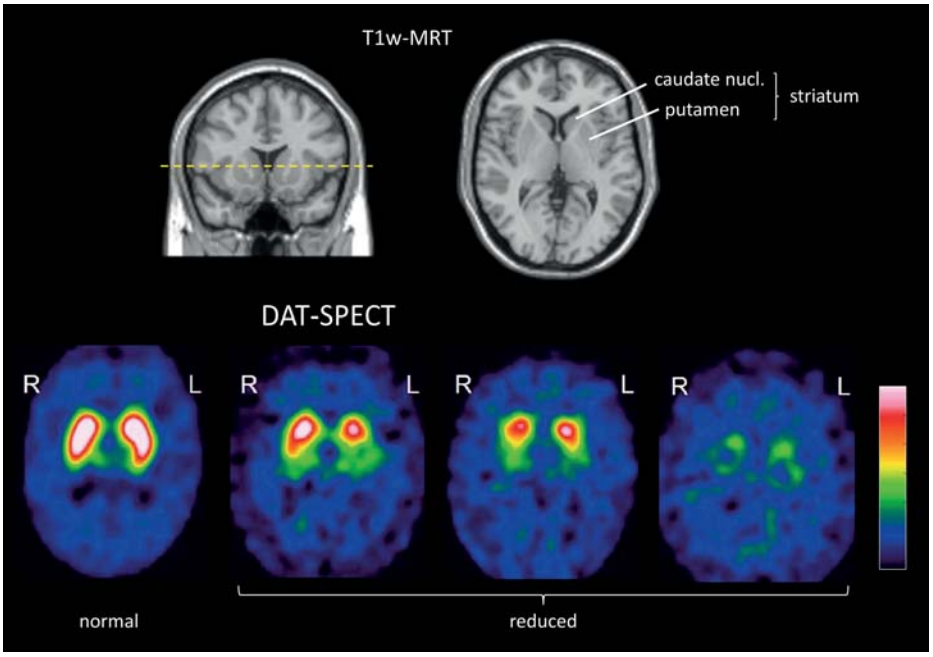

Figure 1: Typical DAT-SPECT findings in patients with idiopathic parkinsonian syndrome (IPS) showing reduced striatal DAT availability compared with a normal findng. The reduction is often left/right asymmetrical, usually more pronounced in the hemisphere that is contralateral to the clinically dominant side of the body (e78). The (posterior) putamen is almost always most strongly affected (e79). Motor symptoms in IPS manifest only after a DAT loss of about 50% in the putamen (14). A strong reduction in tracer uptake in the (contralateral) putamen is therefore the minimum finding on DAT-SPECT in IPS. A reduction that is only slight should as a rule not be seen as an indication of nigrostriatal degeneration (40, e80). The atypical neurodegenerative parkinsonian syndromes, especially PSP and MSA of the Parkinson type, show similar patterns of findings on DAT-SPECT as IPS (9). DAT-SPECT, single photon emission computed tomography with dopamine transporter ligands; MSA, multiple system atrophy; PSP, progressive supranuclear palsy

Prospective studies of the diagnostic accuracy of DAT-SPECT in clinically uncertain parkinsonian or tremor syndromes with postmortem verification are lacking. Studies that used the clinical diagnosis made by movement disorder specialists during the course of the illness as a reference showed a sensitivity of 78–100% (median 93%, 18 studies, of which five were recent, including 1963 patients, *eTable*) and a specificity of 70–100% (median 89%). Some of these studies possibly underestimated the diagnostic accuracy of DAT-SPECT because of the limitations of the clinical diagnosis as standard of truth. This is supported by the fact that the accuracy of DAT-SPECT improves with increasing time to follow-up to obtain the clinical reference diagnosis (11), probably because the clinical diagnostic accuracy improves over time (4). This assumption is also supported by a longitudinal study in which DAT-SPECT after 36 months showed in only two out of 99 patients a discordant finding compared with DAT-SPECT at the start of the study (15). In an annual loss of striatal DAT of 5% (IPS) to 10% (APS) (16), DAT-SPECT after three years would have been able to detect nigrostriatal degeneration that at the time of the initial examination was below the detectability threshold (17). Uncertainty in determining the sensitivity of DAT-SPECT originates not least from the fact that some patients with a clinical diagnosis of a neurodegenerative parkinsonian syndrome present with normal DAT availability according to DAT-SPECT; these patients are referred to as "subjects without evidence of dopaminergic deficit (SWEDD)" (18). Longitudinal studies in which most of the SWEDD had a normal finding on DAT-SPECT even after two to five years hint at clinical overdiagnosis of neurodegenerative parkinsonian syndrome as the most likely explanation for SWEDD (15, 19, e37).

The Movement Disorder Society lists a normal result on DAT-SPECT as an absolute exclusion criterion for the diagnosis of clinically certain or possible IPS (2). A pathological DAT-SPECT result was not included as a supporting criterion for a diagnosis of IPS because DAT-SPECT is not suitable for differentiating IPS from APS (2). For the diagnosis of probable MSA of the cerebellar type a pathological DAT-SPECT result is one of six additional characteristics of which at least one has to be present (3).

After DAT-SPECT, the diagnosis changes in 27–56% of patients with clinically uncertain parkinsonian or tremor syndrome (median 43%, 12 original studies, of these 8 recent ones, including a total of 2719 patients) (*Table*). In 33–72% of patients, DAT-SPECT results in changing treatment (median 43%). In a clinically certain diagnosis of IPS, DAT-SPECT probably affects management much less than in clinically uncertain cases (20).

In sum, high diagnostic accuracy and a relevant effect on the diagnosis and therapy in clinically uncertain parkinsonian or tremor syndromes have been well confirmed as the basis of the guideline recommendations for DAT-SPECT; recent studies have added to the evidence (*eTable*, *Table*). The European IPS guideline recommends DAT-SPECT in the setting of significant diagnostic uncertainty, especially in atypical tremor manifestations (21). According to the British guideline, DAT-SPECT should be considered in case of uncertainty regarding the differentiation of parkinsonian syndrome with nigrostriatal degeneration and essential tremor (22).

TABLE

Original studies of the effect of DAT-SPECT on the diagnosis and treatment of patients with clinically uncertain parkinsonian or tremor syndrome*[1]

Reference	Study design	Number of clinically uncertain cases (n)	Pathological result on DAT-SPECT (%)*[2]	Proportion with change of diagnosis after DAT-SPECT (%)	Proportion with change of treatment*[3] after DAT-SPECT (%)
(e117)	Retrospective, 2 centers	81	69 (n = 261)*[4]	30	35
(e118)	Retrospective, single center	134	59 (n = 173)	N/A	37
(e119)	Retrospective, single center	51	29	N/A	41
(e120)	Prospective, single center, observational study	27	81	N/A	67
(e121)	Retrospective, single center	83	54	43	37
(e122)	Retrospective, single center, patient survey	45	66 (n = 61)	N/A	51
(e123)	Retrospective, single center	57	34 (n = 65)	27 (n = 49)	72
(e124)	Retrospective, single center	423*[5]	64 (n = 516)	N/A	33
(27)	Prospective, multicenter, randomized	116*[6]	52 (n = 102)*[7]	45 (n = 102)*[7]	45
(26)	Retrospective, multicenter, national patient registry in Belgium	1 514	60 (n = 1701)	56 (n = 1559)	55
(23)	Prospective, multicenter, single arm (DAT-SPECT in all patients)	118*[6]	62	52	46
(e116)*[8]	Retrospective, single center	70	63	30	36*[9]
		Total 2719	Median 61 Min–Max 29–81	Median 43 Min–Max 27–56	Median 43 Min–Max 33–72

*[1] Studies including only clinically certain cases (e.g., probable Parkinson's disease) were not included. In studies of clinically uncertain and clinically certain cases, only the clinically uncertain cases were included. In all included studies, DAT-SPECT used the ligand [^{123}I]ioflupane unless otherwise indicated. The interpretation of DAT-SPECT in all studies was based on a visual assessment of the images.

*[2] Where data on the proportions of cases with a pathological result on DAT-SPECT refer to a patient group other than the clinically uncertain cases as per the third column, the size of this group is given in parentheses. As a rule this group includes clinically uncertain cases and clinically certain cases.

*[3] Only changes in treatment (unplanned treatment initiated, avoiding or discontinuing planned treatment, dosage changes). Other changes to patient management (undertaking or cancelling further diagnostic measures, changes to the time interval between presentations/consultations …) were not considered.

*[4] Includes patients without a clinically uncertain parkinsonian or tremor syndrome (ca. 13%)

*[5] Includes patients without a clinically uncertain parkinsonian or tremor syndrome (ca. 37%)

*[6] Efficacy population

*[7] Per protocol population

*[8] This study used the DAT ligand [^{123}I]β-CIT.

*[9] Change in treatment, management, or diagnosis

DAT-SPECT, single photo emission computed tomography (SPECT) using dopamine transporter(DAT) ligands; N/A, not reported in the publication; Max, maximum; Min, minimum

Guideline recommendations for DAT-SPECT relate exclusively to clinically uncertain cases. A clinical uncertain parkinsonian or tremor syndrome is present if at least one of the following criteria is met (23, 24):

- Only one of the three cardinal symptoms rigor, resting tremor, postural instability in addition to akinesia/bradykinesia
- Two cardinal symptoms without akinesia/bradykinesia
- Atypical symptoms
- Only mild symptoms
- Poor response to dopamine substitution treatment
- Very slow/absent or very rapid progression of symptoms
- Atypical age.

The primary suspected diagnoses are immaterial: DAT-SPECT serves the purpose of differentiating parkinsonian syndromes with nigrostriatal degeneration (independently of the cause of the degeneration) from parkinsonian syndromes without nigrostriatal degeneration (also independently of the etiology) in clinically uncertain cases. Application of these criteria for a clinically uncertain parkinsonian or tremor syndrome (explicitly or mutatis mutandis) results in a pretest probability for pathological DAT-SPECT findings of 27–79% (median 60%, *eTable*). Clinical uncertainty regarding the differentiation between IPS and APS is not an indication for DAT-SPECT (23).

In 2015, about 10 000 DAT-SPECT investigations were carried out in Germany (25). Assuming that of these, 1000–2000 were conducted in the setting of

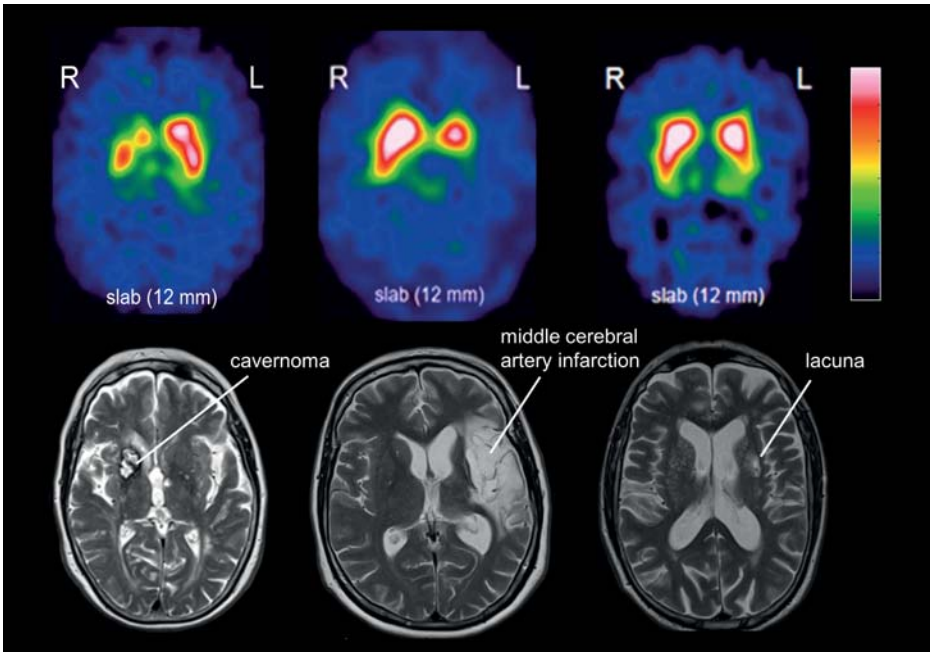

Figure 2: Atypical patterns of findings on DAT-SPECT—for example, reduction of tracer uptake more pronounced in the caudate nucleus than in the putamen—are often caused by vascular lesions. Depending on their localization, vascular lesions can also cause patterns of findings that on DAT-SPECT alone cannot be differentiated from nigrostriatal degeneration. DAT-SPECT should therefore by interpreted in tandem with up-to-date structural images, preferably MRI.
DAT-SPECT, single photon emission computed tomography (SPECT) using dopamine transporter (DAT) ligands; MRI, magnetic resonance imaging

suspected Lewy body dementia (*eBox*), this corresponds to 30% of all patients with new-onset parkinsonism (incidence 33/100 000 per year [e38]). This speaks in favor of adequate use of DAT-SPECT. However, the rate of patients referred for DAT-SPECT when newly presenting with parkinsonism varies strongly between different movement disorder specialists (e39, e40). Model-based analyses of the cost effectiveness of DAT-SPECT assume 20–30% of clinically uncertain cases among all patients with early stage parkinsonian syndrome (26, e41).

The relevant effect of DAT-SPECT in clinically uncertain parkinsonian or tremor syndromes lies in enabling earlier correct diagnosis. As a result, patients benefit from receiving adequate treatment about 1–2 years earlier compared to clinical diagnosis alone (26, e42, e43). In individual cases, however, the time to correct diagnosis of a neurodegenerative parkinsonian syndrome on clinical grounds can be more than 10 years (e44).

Confirmation of the benefit of DAT-SPECT in the diagnostic evaluation of clinically uncertain parkinsonian or tremor syndromes in terms of patient-relevant endpoints—such as mortality, morbidity, and health related quality of life—is pending (27) and will probably only become possible once neuroprotective therapies become available.

For predicting α-synuclein pathology syndrome in patients with idiopathic REM sleep behavior disorder, DAT-SPECT probably yields independent information beyond clinical parameters and other investigations (e45–e48). The prognostic value of DAT-SPECT at very early clinical stages—that is, before the occurrence of motor symptoms—has, however, not been definitively explored. Thus, routine clinical use of DAT-SPECT for this indication cannot be recommended at this time.

In Germany, DAT-SPECT using [^{123}I]ioflupane is also licensed for distinguishing dementia with Lewy bodies from Alzheimer's disease (*eBox*).

Safety

Ioflupane is a cocaine analogue with a high affinity for DAT (e49). For DAT-SPECT, the maximum administered dose is 0.325µg ioflupane, which occupies, at most, 1% of striatal DAT. Typical cocaine effects require at least 60% DAT occupancy to occur (e50).

Temporary adverse effects of a mild or moderate intensity—especially headache and nausea—affect a maximum of 4% of patients (28). In one of 1180 patients, limbic encephalopathy was diagnosed, with a possible causal association with a DAT-SPECT investigation conducted 81 days previously (28). No further indications of severe adverse effects have been documented (28).

Intravenous administration of the recommended amount of radioactivity of 180 MBq [^{123}I]ioflupane (e51) leads to an effective radiation dose of 4.4 millisievert (mSv) (29). The mean effective dose from natural sources of radiation in Germany is 2.1 mSv per year (range 1–10 mSv). The primary risk associated with exposure to low doses of radiation is that of developing a radiation-induced tumor. In an effective radiation dose of 4.4 mSv at age 50 years or older, the lifetime risk of dying from tumor disease thus induced is below 1 : 5000. By comparison, the overall lifetime risk to die from cancer is about 1 : 5 (www.cancer.org/cancer/cancer-basics/lifetime-probability-of-developing-or-dying-from-cancer.html). The mean latency period between radiation exposure and the

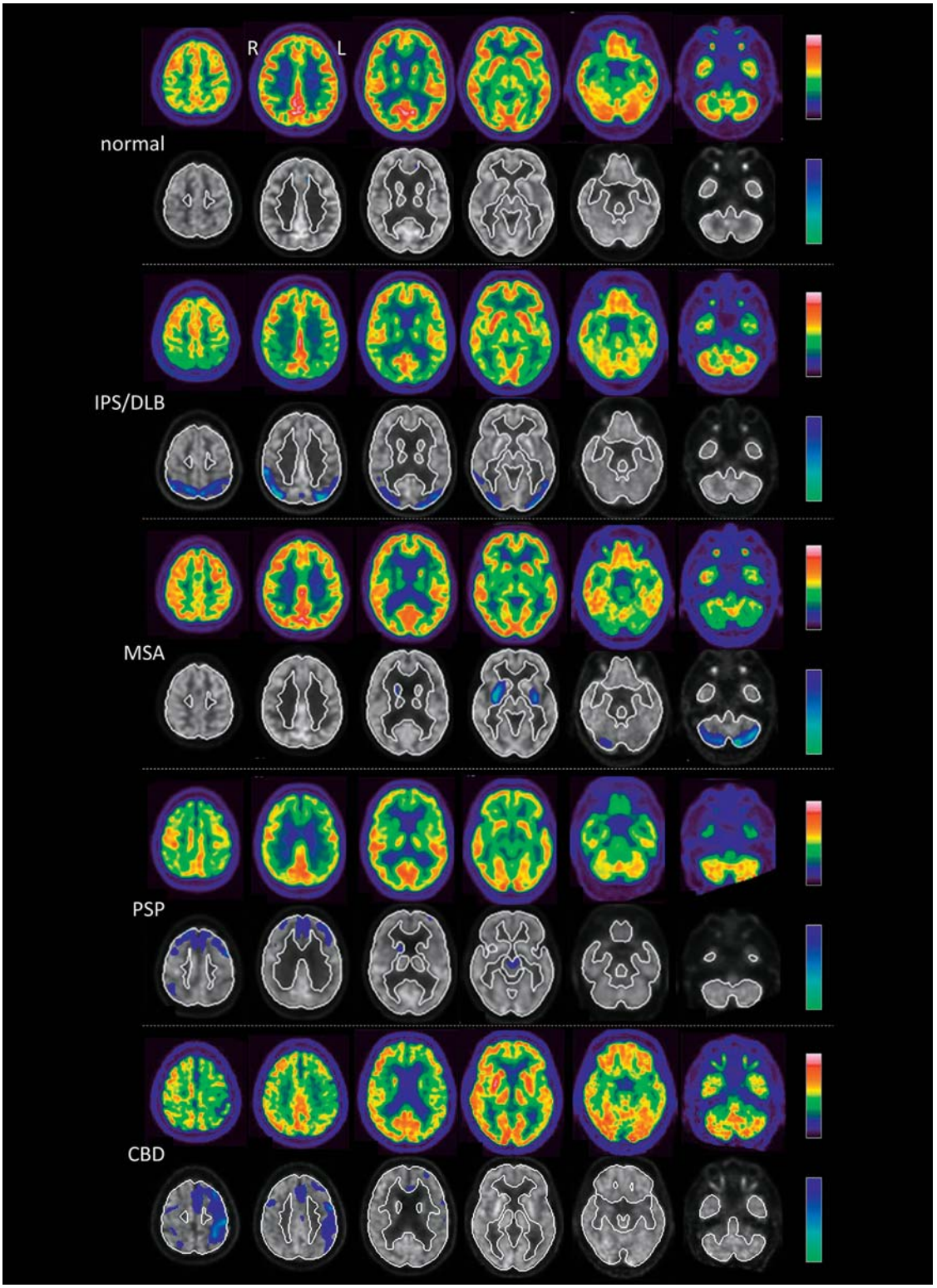

Figure 3: Disease specific FDG-PET results in neurodegenerative parkinsonian syndromes. The respective top line shows selected tomography sections of the FDG image, the bottom line shows the associated statistical map from voxel-based testing of the same patient compared with healthy persons (a statistically significant reduction in FDG uptake is marked in blue). Patients with a disorder on the Lewy body spectrum often (in IPS) or regularly (in IPS with dementia and dementia of the Lewy body type [DLB]) present with hypometabolism in the posterior brain regions and relative hypermetabolism in the putamen, motor cortex, and cerebellum (33). MSA is characterized by a reduction in FDG uptake in the putamen and/or cerebellum (e81). In PSP, regional hypometabolism can be observed in the medial frontal region, including the anterior cingulate cortex, in the dorsolateral frontal region, as well as in the caudate nucleus, thalamus, and brain stem (32, e73). In pathologically confirmed CBD, FDG-PET shows hypometabolism in the frontoparietal cortex and the striatum and thalamus, contralateral to the clinically more affected side of the body, as in the example shown (35, e73, e74, e77).

occurrence of an induced tumor is eight years for leukemia and thyroid cancer; for all other tumor diseases it is more than 10 years (www.bfs.de/DE/themen/ion/wirkung/krebs/einfuehrung/einfuehrung.html). By comparison, the median survival after a diagnosis of APS is 3–5 years (e52, e53).

Limitations

Relevant medication interactions are rare for DAT-SPECT. Before the investigation, only substances with direct DAT inhibition have to be discontinued: cocaine, amphetamine, methamphetamine, dextroamphetamine, methylphenidate, modafinil, diethylpropion, mazindol, phentermine, bupropion, venlafaxine, radafaxine, fentanyl, ketamine, isoflurane, and phenyl-cyclidine-piperidine (30). The antidepressants venlafaxine and bupropion are of particular practical relevance. Antipsychotics do not have any relevant effect on DAT-SPECT and therefore do not have to be discontinued (30, e54). Smoking does not affect DAT-SPECT either (e55).

Because of partly lacking nigrostriatal degeneration in CBD, the sensitivity of DAT-SPECT for detecting CBD is limited (e56–e58).

Lesions in the striatum or brainstem result in a defect in striatal tracer uptake on DAT-SPECT, which depending on its location cannot be distinguished from the typical pattern of nigrostriatal degeneration (e59, e60) (*Figure 2*). In order to avoid a misinterpretation of vascular lesions as an indication of nigrostriatal degeneration, DAT-SPECT should be interpreted in tandem with up-to-date structural imaging, preferably cranial MRI (31).

DAT-SPECT is not suitable for differentiating the various neurodegenerative parkinsonian syndromes (IPS, MSA, PSP, CBD) from each other (9, e61). The guideline names cerebral PET scanning using the glucose analogue [^{18}F]fluorodeoxyglucose (FDG) as the best modality for this purpose (1).

FDG-PET in the differential diagnostic evaluation of neurodegenerative parkinsonian syndromes

FDG-PET of the brain depicts the regional cerebral glucose metabolism, which is closely connected to neuronal activity (e62–e64). Thus, cerebral FDG-PET is a marker for regional neuronal dysfunction/degeneration. The strength of FDG-PET in the differential diagnostic evaluation of neurodegenerative parkinsonian syndromes lies in the identification of disease-specific patterns of findings on PET (*Figure 3*). To support the visual assessment of the PET images, voxel-based evaluations are used which compare the FDG-PET image of the patient with those of healthy persons voxel by voxel, in the simplest scenario by using z scores or t tests (e65, e66). The result of the voxel-based test can be superimposed on tomography sections (*Figure 3*). Voxel-based testing improves the accuracy of FDG-PET in detecting neurodegenerative disorders for inexperienced persons interpreting the findings as well as for experts (e67).

A recent meta-analysis of FDG-PET to distinguish APS (MSA, PSP, CBD) from IPS showed a sensitivity of 91% (95% confidence interval [72; 98]) and a specificity of 91% [70; 98] in relation to the clinical diagnosis made by movement disorder specialists after a period of 1–2 years after the PET investigation (32). At the time of the PET, the clinical diagnosis was usually uncertain (32). FDG-PET offered good accuracy for differentiating MSA from PSP and CBD (33). Differentiating PSP from CBD was less successful, in particular PSP was miscategorized as CBD (34), which is consistent with the wide overlap between the tauopathies PSP and CBD (e68–e71). New approaches to evaluating FDG-PET on the basis of voxel-based analysis of covariance allow for automatic and thus user-independent differentiation between the different neurodegenerative parkinsonian syndromes (35).

Longitudinal studies demonstrate the benefit of FDG-PET for predicting dementia in IPS (36, e72) and survival in suspected APS (37).

In view of the inherent uncertainties of the clinical differentiation of APS from IPS and APS among themselves, prospective studies with clinically relevant patient populations and postmortem verification of the diagnosis are needed for the further validation of FDG-PET for the differential diagnostic evaluation of neurodegenerative parkinsonian syndromes (38). Existing reports of case series with postmortem verification (35, e73–e77) are not sufficient, even though they confirm the disease-specific patterns of findings from patient populations with a clinical diagnosis.

For further discussion of the role of FDG-PET in the diagnostic evaluation of neurodegenerative parkinsonian syndromes we refer readers to the recent literature (32, 38, 39).

Conflict of interest statement

Dr Buchert received financial support for conducting advanced training courses from GE Healthcare. He received study support from Pinax Pharma and Siemens. He received a honorarium from ABX-CRO for composing a manuscript.

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Prof. Gallinat received support for events or lectures from Lundbeck, Janssen-Cilag, Lilly, and Otsuka.

Dr. Apostolova declares that no conflict of interest exists.

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Key messages

- Single photon emission computed tomography (SPECT) using dopamine transporter (DAT) ligands has been well validated as a marker for nigrostriatal degeneration by comparison with postmortem examinations.
- DAT-SPECT enables detection of nigrostriatal degeneration in patients with clinically uncertain parkinsonian or tremor syndrome with good sensitivity and specificity (around 90% each).
- After DAT-SPECT, the diagnosis is changed in 27–56% (median 43%) of patients with clinically uncertain parkinsonian or tremor syndrome, and treatment is changed in 33–72% (median 43%).
- DAT-SPECT enables the differentiation of dementia with Lewy bodies from Alzheimer's dementia with a specificity of about 90% and a sensitivity of about 80%.
- FDG-PET enables the differentiation of the atypical neurogenerative parkinsonian syndromes from idiopathic parkinsonian syndrome in clinically uncertain cases with good specificity and sensitivity (both about 90%). There is a need for studies with neuropathological verification of the diagnosis as standard of truth.

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Corresponding author
Dr. rer. nat. Ralph Buchert
Klinik und Poliklinik für Diagnostische und Interventionelle Radiologie und Nuklearmedizin, Universitätsklinikum Hamburg-Eppendorf
Martinistr. 52, 20246 Hamburg, Germany
r.buchert@uke.de

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Nuclear Imaging in the Diagnosis of Clinically Uncertain Parkinsonian Syndromes

by Ralph Buchert, Carsten Buhmann, Ivayla Apostolova, Philipp T. Meyer, and Jürgen Gallinat

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eTABLE

Original studies of the diagnostic accuracy of DAT-SPECT for detecting nigrostriatal degeneration in patients with clinically uncertain parkinsonian or tremor syndrome and a clinical diagnosis based on clinical follow-up as standard of truth*1

Reference	Study design	Number of clinically uncertain cases (n)	Duration of clinical follow-up after DAT-SPECT (months)	Pathological DAT-SPECT (%)	SPECT analysis	Sensitivity (%) [95-%-CI]	Specificity (%) [95-%-CI]
(e105)	Retrospective, single center	138	29 ± 16	58	Visual	92	83
(e106)	Retrospective, single center	122	27 ± 15	66	Semi-quantitative*2	94	95
(e33)	Retrospective, multicenter	102*3	N/A	54	Visual	86 [74; 94]	88 [75; 96]
(e33)	Retrospective, multicenter	102*4	N/A	55	Visual	88 [76; 95]	89 [75; 96]
(e107)	3 centers	220	24–48	55	Semi-quantitative*2	83 [76; 89]	91 [83; 97]
(11)	Prospective, multicenter, randomized	92*5	12	53	Visual	94 [83; 99]	95 [84; 99]
(e108)	Prospective, 2 centers	176	24	61	Visual	84	81
(e109)*6	Prospective, single center	189	20 ± 13 (4–67)	66	Semi-quantitative*7	92	83
(e110)*8	Single center	15	17–32	53	Semi-quantitative*9	100	70
(15)	Prospective, multicenter	99	36	58	Visual	78 [66; 88]*10	97 [83; 100]*10
(e40)	Single center	190	18 (4–39)	58	Semi-quantitative*11	80	92
(e111)	Retrospective, single center	55	≥ 6	78	Semi-quantitative*11	98	100
(e112)	Prospective, multicenter	77	24 ± 6	69	Visual	98	77
(e113)	Retrospective, single center	72	16 ± 7 (6–24)	79	Semi-quantitative*2	93	100
(e114)*12	Single center	177	≥ 24	68	Semi-quantitative*2	99	81
(e115)*12	Prospective, single center	35	6	74	Visual	96	80
(e116)*12	Retrospective, single center	69	"Months to years"	64	Visual	93*13	88*13
(24)	N/A	33	38 ± 7 (25–51)	27	Semi-quantitative*7	82	100
		Total 1963		Median 60 Min–Max 27–79		Median 93 Min–Max 78–100	Median 89 Min–Max 70–100

*1 Meta-analyses (17, e54, e97, e98) and summarizing analyses (e99) were not included. Original studies of exclusively clinically certain cases (eg, probable Parkinson's disease) were not included either (e100–e104). In studies with clinically uncertain and clinically certain cases, only the clinically uncertain cases were included. In all included studies, DAT-SPECT used the ligand [^{123}I]ioflupane unless otherwise indicated.
*2 Specific binding ratio in the putamen (contralateral to the clinically dominant side of the body or the minimum of both hemispheres), not cross validated
*3 Caucasian/white
*4 Non-caucasian/white
*5 Study E in (11)
*6 This study used the DAT ligand [^{123}I]PE2I.
*7 Specific binding ratio in the putamen (contralateral to the clinically dominant side of the body or the minimum of both hemispheres), predefined cut-off value
*8 This study used the DAT ligand [^{99m}Tc]TRODAT-1.
*9 Specific binding ratio in the striatum (contralateral to the clinically dominant side of the body or the minimum of both hemispheres), predefined cut-off value
*10 Clinical diagnosis after 36 months as the standard of truth. With repeated DAT-SPECT after 36 months as standard of truth: sensitivity = specificity = 98%
*11 Specific binding ratio in the putamen, predefined cut-off value
*12 This study used the DAT ligand [^{123}I]ß-CIT
*13 Borderline results of DAT-SPECT (n = 4) were classified as normal.
DAT-SPECT, single photon emission computed tomography (SPECT) using dopamine transporter (DAT) ligands; CI, confidence interval; N/A, not reported in the publication; Max, maximum; Min, minimum

eBOX

DAT-SPECT in the differentiation of dementia with Lewy bodies from Alzheimer's disease

The clinical relevance of differentiating dementia with Lewy bodies (DLB) from Alzheimer's disease (which the license approval of [^{123}I]ioflupane relates to, even though in clinical practice it is certainly the detection of Alzheimer's dementia (AD)—i.e., Alzheimer's disease at the dementia stage—that is of greatest relevance) lies in differences in the disease course and the symptoms that are to be expected, as well as the much increased risk of severe adverse effects of neuroleptic drugs in DLB (e82). In postmortem studies, DLB is diagnosed about three times more often than in clinical prevalence studies (≥ 15% [e83] versus 4–5% [e84]). This suggests that DLB is considerably underdiagnosed in clinical routine.

An early multicenter phase III trial with a clinical diagnosis as the standard of truth showed a sensitivity of 77.7% (95% confidence interval [64.1; 88.3]) and a specificity of 90.4% [82.1; 95.5] for single photon emission computed tomography (SPECT) with the dopamine transporter (DAT) ligand [^{123}I]ioflupane in terms of differentiating DLB from other dementia types (e85). Since then, several studies have been conducted that used a neuropathological diagnosis as standard of truth. In a study that compared 7 patients with a neuropathological diagnosis of DLB with 12 patients with a neuropathological diagnosis of AD, DAT-SPECT had a sensitivity of 86% [42; 100] and a specificity of 83% [52; 98] for the detection of DLB, which was clearly better than the clinical diagnosis (sensitivity 75%, specificity 42%) (e86–e88). With reference to this study, the authors of a systematic review for the Cochrane Collaboration concluded in spite of the small number of patients that DAT-SPECT is probably superior to a clinical diagnosis of DLB in patients with dementia, and that the clinical diagnosis is therefore not suitable as a standard of truth for determining the diagnostic accuracy of DAT-SPECT (e87). A recent follow-up study using neuropathology as standard of truth compared 30 DLB patients with 25 patients with pure AD (n = 21) or frontotemporal lobe degeneration (n = 4; among these, 1 case of corticobasal degeneration) and found a sensitivity of 80% [62; 92] and a specificity of 92% [74; 99] for DAT-SPECT in the diagnosis of DLB (e89). Compared with the clinical diagnosis (sensitivity 87% [70; 96], specificity 72% [51; 88]), DAT-SPECT therefore had a much better specificity and a slightly lower sensitivity (e89). The neocortical DLB subtype is under discussion as the possible cause of the lower sensitivity of DAT-SPECT. In the neocortical DLB subtype, the α-synuclein pathology spares the brain stem, at least in the early stages (e90). This hypothesis was supported by a recent longitudinal DAT-SPECT study in 5 patients with a clinical diagnosis of probable DLB and a normal result on initial DAT-SPECT, in which repeated SPECT over time showed a reduction in striatal DAT in all patients after a mean period of 1.5 years (e91). An additional recent study using neuropathology as the standard of truth found a reduction in the striatal DAT density in 11 of 12 DLB patients, and a normal value in 5 of 6 non-DLB patients (e92).

In DLB, cases with a uniform reduction in DAT availability in the entire striatum have also been observed—that is, without the focus on the putamen, which is typical for the idiopathic parkinsonian syndrome. This should be considered when assessing DAT-SPECT for differentiating DLB from AD (e93).

A recent literature search to assess DAT-SPECT as a biomarker for differentiating DLB from AD that used a conceptual framework for the validation of biomarkers showed that the evidence for the analytical and clinical validity is sufficient, whereas the proof of the clinical usefulness of DAT-SPECT for this indicaton has largely not been rendered (e94).

DAT-SPECT is suitable for differentiating dementia with Lewy bodies from Alzheimer's disease in particular—for the differentiation from other dementias it may have limitations (e95).

The current diagnostic criteria for DLB list a pathological result of DAT-SPECT as an indicative biomarker, which, in combination with dementia and a clinical key characteristic justifies the diagnosis of probable DLB (e96).