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Clinical Note: How I Examine My Patient

Impact of DaTscan Imaging on Clinical Decision Making in Clinically Uncertain Parkinson's Disease

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Abstract.
Background: The diagnosis of Parkinson's disease (PD) is primarily clinical, but in cases of diagnostic uncertainty, evaluation of nigrostriatal dopaminergic degeneration (NSDD) by imaging of the dopamine transporter using DaTscan with single-photon emission computed tomography (SPECT) brain imaging may be helpful.
Objective/Methods: In the current paper, we describe clinical scenarios for which DaTscan imaging was used in a prospective case series of 201 consecutive patients in whom a movement disorder specialist ordered DaTscan imaging to clarify NSDD. We describe the impact of DaTscan results on changing or confirming pre-DaTscan clinical diagnosis and on post-DaTscan treatment changes.
Results/Conclusion: DaTscan imaging can be useful in several clinical scenarios to determine if NSDD is present. These include in patients with early subtle symptoms, suboptimal response to levodopa, prominent action tremor, drug-induced parkinsonism, and in patients with lower extremity or other less common parkinsonism clinical presentations. We also found DaTscan imaging to be useful to determine underlying NSDD in patients with PD diagnosis for 3-5 years but without apparent clinical progression or development of motor fluctuations. Overall, in 201 consecutive patients with clinically questionable NSDD, DaTscan was abnormal in 58.7% of patients, normal in 37.8%, and inconclusive in 3.5%. DaTscan imaging changed clinical diagnosis in 39.8% of patients and led to medication therapy changes in 70.1% of patients.

INTRODUCTION OF THE CLINICAL DILEMMA

The diagnosis of Parkinson's disease (PD) has traditionally been based on clinical phenomenology [1]. However, around two in every ten patients are initially misdiagnosed, even at experienced PD centers [2, 3]. (^{123}I)Ioflupane (Iodine-123-fluoropropyl (FP)-carbomethoxy– 3β-(4-iodophenyltropane) (commercially available as DaTscan™, GE Healthcare) is a radiopharmaceutical indicated for striatal dopamine transporter visualization using SPECT brain imaging to assist in the evaluation of adult patients with suspected parkinsonian syndromes.

DaTscan is often cited as being most useful to distinguish between PD and essential tremor (ET) or between PD and drug-induced parkinsonism [4, 5]. However, there are several other clinical scenarios where it may be useful (Table 1) [6]. In our routine practice, we have used DaTscan in our patients when there is uncertainty if clinical parkinsonism reflects nigrostriatal dopaminergic degeneration (NSDD), leading to indeterminate diagnostic and/or treatment shared clinical decision making. Uncertainty of NS DD may delay an accurate diagnosis of PD and other degenerative disorders with NSDD and may lead patients to seek additional clinical evaluations and

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Table 1
Clinical scenarios in which NSDD may be uncertain

1: Patient with early, subtle motor signs on examination
2: Patient with parkinsonism, but has suboptimal response to medication
3: Patient with prominent action tremor, interfering with examination of bradykinesia, rest tremor, and/or rigidity
4: Patient with clinical diagnosis of PD who has been clinically stable for initial 3–5 years without increasing medication nor development of motor fluctuations
5: Parkinsonism with recent exposure to dopamine receptor blocking medication
6: Predominant lower extremity parkinsonism or other neurologic disorders with parkinsonism where NSDD is possible

other testing. Clinical uncertainty of NSDD may also lead to hesitation in starting, increasing, or stopping medication therapy amongst physicians and patients.

DESCRIPTION OF THE TEST

Following intravenous injection, the radioligand Ioflupane distributes to the striatum, where it binds with high affinity to the presynaptic dopamine transporter protein to allow SPECT imaging of the radioligand within 3–6 hours after injection. The major utility of DaTscan imaging is the assistance it provides in distinguishing between NSDD (abnormal scan) and non-NSDD (normal scan). Visual differentiation between normal and abnormal scans is assessed by the shape and intensity of the striatal (caudate and putaminal) signal.

We performed a retrospective analysis of 201 consecutive de-identified patients in whom a movement disorder specialist ordered DaTscan imaging to determine NSDD to clarify diagnosis prior to making treatment change. Prior to DaTscan imaging, the clinical course, levodopa response, and number of cardinal motor signs (bradykinesia, tremor, rigidity) were reviewed, and the clinical probability of PD diagnosis (as assessed by movement disorder specialist based on UK Brain Bank Criteria [7]) was recorded. Quantitative software is also available but was not utilized in this analysis. Patients in this series had a commercially available DaTscan at an imaging center near their home. Visual analysis of DaTscan imaging was performed independently by a (neuro)radiologist at the imaging center and by a PD specialist, prior to review of clinical impression. Whenever DaTscan interpretation diverged, images were reviewed again, and if interpretations remained discordant then DaTscan was recorded as inconclusive.

DISCUSSION OF RESULTS

In our patients (mean age 77 years, range 50–91 years), the most common clinical scenarios for DaTscan imaging were early subtle motor signs ($n = 59$, 29.4%) and suboptimal levodopa response ($n = 47$, 23.4%). Other common clinical scenarios included prominent action tremor interfering with clinical examination ($n = 33$, 16.4%), recent antipsychotic medication ($n = 24$, 11.9%), and PD diagnosis without progression over > 3-5 years ($n = 28$, 13.9%). A final group of patients included predominant lower extremity parkinsonism and other atypical presentations ($n = 10$, 5.0%). The mean number of cardinal motor signs was 2.4 (5.5% had one, 48.8% had two, and 45.8% had three cardinal motor signs). The number of cardinal motor signs were lowest in subgroup with early subtle parkinsonism (mean of 2.33), and highest in subgroup with drug exposure (mean of 2.74). The clinically assessed probability of PD diagnosis was 50%, 75%, 90%, or 95% probable in 17.9%, 49.3%, 29.9%, and 3.0% of patients, respectively.

Overall, DaTscan was abnormal in 58.7% of patients, normal in 37.8%, and inconclusive in 3.5% (Table 2). DaTscan was abnormal in nearly two-thirds of patients with early subtle parkinsonism or with suboptimal levodopa response, and in approximately 50% of other clinical scenarios. Interestingly, inconclusive DaTscan was most common when prominent action tremor was present (12%). Abnormal DaTscan was more frequent with increasing number of cardinal motor signs, although DaTscan was normal in 28% of patients with all three cardinal motor signs. Abnormal DaTscan also increased with increasing probability of clinical PD diagnosis, however clinical assessment tended to overestimate PD diagnosis; 20% of patients clinically assessed to have 90% probability of PD diagnosis, had normal DaTscan imaging.

IMPACT ON DIAGNOSIS AND TREATMENT

After DaTscan imaging, changes to the pre-DaTscan clinical diagnosis and medication regimen were assessed. Table 3 shows the impact of DaTscan imaging per clinical scenario of uncertain NSDD.

Table 2
DaTscan findings per scenario, clinically assessed probability of PD diagnosis and number of cardinal signs

	N (%)	Abnormal DaTscan, N (%)	Normal DaTscan, N (%)	Inconclusive DaTscan, N (%)
Overall	201 (100.0%)	118 (58.7%)	76 (37.8%)	7 (3.5%)
Clinical scenario				
Early, subtle motor signs	59 (29.4%)	39 (66.1%)	18 (30.5%)	2 (3.4%)
Suboptimal levodopa response	47 (23.4%)	30 (63.8%)	16 (34.0%)	1 (2.1%)
Prominent action tremor	33 (16.4%)	17 (51.5%)	12 (36.4%)	4 (12.1%)
Stable disease for > 3-5 years	28 (13.9%)	15 (53.6%)	13 (46.4%)	0
Recent dopamine antagonist exposure	24 (11.9%)	12 (50.0%)	12 (50.0%)	0
Lower extremity parkinsonism or other diagnosis	10 (5.0%)	5 (50.0%)	5 (50.0%)	0
Clinically assessed probability of PD diagnosis				
50%	36 (17.9%)	7 (19.4%)	27 (75.0%)	2 (5.6%)
75%	99 (49.3%)	57 (57.6%)	37 (37.4%)	5 (5.1%)
90%	60 (29.9%)	48 (80.0%)	12 (20.0%)	0
95%	6 (3.0%)	6 (100.0%)	0	0
Number of cardinal motor signs (bradykinesia, rest tremor, and rigidity)				
1 cardinal sign	11 (5.5%)	1 (9.1%)	8 (72.7%)	2 (18.2%)
2 cardinal signs	98 (48.8%)	54 (55.1%)	42 (42.9%)	3 (3.1%)
3 cardinal signs	92 (45.8%)	63 (68.5%)	26 (28.3%)	2 (2.2%)

Table 3
Impact of DaTscan imaging per clinical scenario of uncertain nigrostriatal degeneration

	Mean age (years)	Mean number of cardinal signs	Diagnosis changed N (%)[a]	Treatment changed N (%)[b]
Overall, N = 201 (100%)	77	2.40	80 (39.8%)	141 (70.1%)
Early, subtle motor signs, N = 59 (29.4%)	75	2.33	21 (35.6%)	36 (61.0%)
Suboptimal levodopa response, N = 47 (23.4%)	78	2.38	17 (36.2%)	32 (68.1%)
Prominent action tremor, N = 33 (16.4%)	77	2.52	13 (39.4%)	23 (69.7%)
Stable disease for > 3–5 years, N = 28 (13.9%)	76	2.57	11 (39.3%)	22 (78.6%)
Recent dopamine antagonist exposure, N = 24 (11.9%)	73	2.74	12 (50.0%)	20 (83.3%)
Lower extremity parkinsonism or other diagnosis, N = 10 (5.0%)	80	2.40	6 (60.0%)	8 (80.0%)

(a) Among patients with changed diagnosis, DaTscan was normal in 75.0%, abnormal in 17.5%, and inconclusive in 7.5%. Among patients with confirmed diagnosis, DaTscan was abnormal in 86.0%, normal in 13.2%, and inconclusive in 0.8% (b) DaTscan changed medication therapy in 70.1% of patients (included stopping (15.9%), starting (23.9%), or switching (30.3%) medication). In 29.9% of patients, treatment was unchanged (included continuing (18.4%) or not starting (11.4%) medication).

Overall, 55.2% of patients had their pre-DaTscan diagnosis confirmed, and 39.8% of patients had their pre-DaTscan diagnosis changed; an additional 5.0% of patients had two diagnoses confirmed. Of those who had their diagnosis changed, most (75.0%) had been initially assessed as having a PD diagnosis reflecting NSDD, but DaTscan was normal indicating another diagnosis [1]. In contrast, DaTscan was abnormal in 79% of patients when pre-DaTscan diagnosis was confirmed. Over 35% of patients in each clinical scenario had a change in diagnosis.

DaTscan imaging prompted treatment change in 70.1% of patients (started medication 23.9%, switched medication 30.3%, stopped medication 15.9%). Amongst patients with a change in pre-DaTscan medication therapy, DaTscan was abnormal in 62.4%. Medication was unchanged in 18.4% of patients, and a medication considered pre-DaTscan was not started after DaTscan in 11.4% of patients. Most patients with a clearly normal (67.1%)/abnormal (74.6%) DaTscan had treatment changed, but only 28.6% of inconclusive DaTscan led to a change in treatment.

Over 60% of patients in each clinical scenario had a change in treatment.

CONCLUSIONS

Our experience is the largest series reported to date of the use of DaTscan imaging in routine clinical practice. Our results are consistent with prior, smaller, single center reports [8–13] that highlight common clinical scenarios where identification of NSDD can help to clarify clinical diagnosis and treatment decisions [6]. In general, an abnormal DaTscan predicted a treatment change when NSDD was uncertain, and a normal DaTscan predicted a change in diagnosis.

DaTscan imaging can be useful in patients where the clinical query is whether PD is emerging in a patient with ET or recent exposure to dopamine receptor blocking medication, because NSDD is present in PD but not ET nor drug-induced parkinsonism. Interestingly, while DaTscan imaging distinguished between drug-induced parkinsonism and PD, there were 12% DaTscan that were inconclusive in distinguishing NSDD in PD from non-NSDD in patients with prominent action tremor, similar to pivotal trials. Our results also suggest DaTscan can be used in patients in whom there is uncertainty if clinical parkinsonism reflects NSDD, such as in patients with mild or inconsistent parkinsonism despite detailed examination. This may help to avoid repeated evaluations over time, as well as unneeded investigations into other clinical diagnoses prompted by nonmotor symptoms. DaTscan imaging of NSDD can also be helpful in patients with parkinsonism who have a suboptimal response to levodopa to help distinguish from other disorders without NSDD [6]. As described in recent MDS criteria, a normal DaTscan excludes a diagnosis of PD, and the absence of levodopa response cannot be counted as an exclusion criterion when a patient has mild PD symptoms, been previously untreated, or who has received < 600 mg levodopa [1]. In these patients, DaTscan confirmation of NSDD can be used to help decide whether to continue dopaminergic treatment in these patients.

Another common clinical scenario were patients who had been diagnosed with PD but did not have clinical progression of parkinsonism over 3-5 years of follow-up. In these patients, we found that 46% had normal DaTscan imaging without NSDD, indicating an incorrect diagnosis of PD. In these patients, continuing dopaminergic replacement therapies is unnecessary. This is consistent with other studies that highlight that inaccuracy of initial PD diagnosis is not uncommon [12].

Our results highlight clinical scenarios in which DaTscan imaging in patients with uncertain NSDD may help to improve diagnostic accuracy. Abnormal DaTscan imaging increased with increasing clinical probability of PD and number of cardinal motor signs present. These results also indicate an unexpectedly high impact of DaTscan imaging on our medication treatment decision making. Overall, DaTscan imaging was a useful adjunct to clinical decision making. These results may suggest a role for DaTscan imaging in personalized precision medicine approaches to treatment of patients in whom NSDD is uncertain.

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CONFLICT OF INTEREST

Jonathan R. Isaacson has no conflicts to report. Salima Brillman reports consultant and/or promotional speaker on behalf of Abbvie, Acadia, Acorda, Amneal, Cala, GE Healthcare, Kyowa Kirin, Lundbeck, Sunovion, Supernus, Teva, and US World Meds. Nisha Chhabria reports honoraria from research grants and/or promotional speaker on behalf of Abbvie, Acadia, Acorda, Adamas, Amneal, Enterin, Lundbeck, Sage, Sunovion, Supernus. Stuart H. Isaacson reports honoraria for CME, consultant, research grants, and/or promotional speaker on behalf of Abbvie, Acadia, Acorda, Adamas, Addex, Affiris, Alexva, Allergan, Amarantus, Amneal, Aptinyx, Axial, Axovant, Benevolent, Biogen, Britannia, Cadent, Cala, Cerecor, Cerevel, Cipla, Eli Lilly, Enterin, GE Healthcare, Global Kinetics, Impax, Impel, Intec Pharma, Ipsen, Jazz, Kyowa, Lundbeck, Merz, Michael J. Fox Foundation, Mitsubishi Tanabe, Neuralys, Neurocrine, Neuroderm, Parkinson Study Group, Pharma2B, Prilenia, Promentis, Revance, Roche, Sanofi, Sunovion, Sun Pharma, Supernus, Teva, Theravance, UCB, Zambon

REFERENCES

[1] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday

G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G (2015) MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* **30**, 1591-1601.

[2] Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G (2016) Accuracy of clinical diagnosis of Parkinson disease: A systematic review and meta-analysis. *Neurology* **86**, 566-576.

[3] Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ (2002) The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain* **125**, 861-870.

[4] de la Fuente-Fernandez R (2012) Role of DaTSCAN and clinical diagnosis in Parkinson disease. *Neurology* **78**, 696-701.

[5] Kagi G, Bhatia KP, Tolosa E (2010) The role of DAT-SPECT in movement disorders. *J Neurol Neurosurg Psychiatry* **81**, 5-12.

[6] Isaacson SH, Fisher S, Gupta F, Hermanowicz N, Kremens DE, Lew MF, Marek K, Pahwa R, Russell DS, Seibyl J (2017) Clinical utility of DaTscan imaging in the evaluation of patients with parkinsonism: A US perspective. *Expert Rev Neurother* **17**, 219-225.

[7] Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* **55**, 181-184.

[8] Sadasivan S, Friedman JH (2015) Experience with DaTscan at a tertiary referral center. *Parkinsonism Relat Disord* **21**, 42-45.

[9] Bega D, Gonzalez-Latapi P, Zadikoff C, Spies W, Simuni T (2015) Is there a role for DAT-SPECT imaging in a specialty movement disorders practice? *Neurodegener Dis* **15**, 81-86.

[10] Oravivattanakul S, Benchaya L, Wu G, Ahmed A, Itin I, Cooper S, Gostkowski M, Rudolph J, Appleby J, Sweeney P, Fernandez H (2015) Dopamine transporter (DaT) scan utilization in a movement disorder center. *Mov Disord Clin Pract* **3**, 1-5.

[11] Gayed I, Joseph U, Fanous M, Wan D, Schiess M, Ondo W, Won KS (2015) The impact of DaTscan in the diagnosis of Parkinson disease. *Clin Nucl Med* **40**, 390-393.

[12] Coarelli G, Garcin B, Roze E, Vidailhet M, Degos B (2019) Invalidation of Parkinson's disease diagnosis after years of follow-up based on clinical, radiological and neurophysiological examination. *J Neurol Sci* **406**, 116454.

[13] Graebner AK, Tarsy D, Shih LC, Vanderhorst V, Kulkarni O, Kaplan S, Simon DK (2017) Clinical impact of 123I-Ioflupane SPECT (DaTscan) in a movement disorder center. *Neurodegener Dis* **17**, 38-43.