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Olfactory Impairment Predicts Underlying Dopaminergic Deficit in Presumed Drug-Induced Parkinsonism

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Abstract: Drug-induced parkinsonism (DIP) is common, and the motor symptoms can be indistinguishable from Parkinson's disease (PD). When symptoms persist after drug withdrawal, this may represent "unmasking" of underlying PD. We previously reported that hyposmia, a common nonmotor feature of PD, was associated with persistent DIP. Here, we report on a series of 33 consecutive patients who underwent dopamine transporter imaging to evaluate DIP. We examined the clinical correlates of underlying dopaminergic denervation by comparing subjects with normal and abnormal scans. Imaging was abnormal in 7 of 33 (21%) cases. Motor features were similar in patients with normal and abnormal scans. Olfactory testing was available for 30 subjects and was concordant with imaging in 27 of 30 (odds ratio = 63; 95% confidence interval: 4.8–820; $P = 0.002$). Olfactory testing may be a simple screen to help identify DIP patients with underlying dopaminergic denervation, consistent with unmasking of incipient PD.

Parkinson's disease (PD) can be mimicked by drug-induced Parkinsonism (DIP)—most commonly associated with dopamine receptor blocking antipsychotic drugs (AP). Parkinsonism occurs in 10% to 20% of patients exposed to AP, and DIP is the second-most common cause of parkinsonism, after PD, in population studies.[1] DIP can be clinically indistinguishable from PD, resulting in diagnostic and therapeutic challenges.

DIP often resolves after removing the offending agent, but symptoms persist for more than 3 months in 11% to 60% of patients.[2,3] Persistent DIP or a sustained response to levodopa may differentiate underlying PD. However, withdrawal of psychiatric drugs or potential exacerbation of psychiatric symptoms by dopaminergics make empiric interventions undesirable when the diagnosis is uncertain. Furthermore, clinical response alone can be unreliable given that subjects with persistent DIP for 6 months can have normal dopamine transporter (DAT) imaging (DAT-SPECT [single-photon emission computed tomography]),[4] and brainstem Lewy pathology has been documented in subjects who died (of unrelated causes) soon after their symptoms resolved.[5] Nonmotor features of PD, including olfactory, mood, autonomic, and sleep symptoms, which may not arise from dopmaminergic blockade alone, could help differentiate the conditions, and we have previously reported worse olfaction in patients with persistent DIP.[6]

Functional imaging modalities, including DAT-SPECT, have high diagnostic efficacy to differentiate degenerative nigrostriatal parkinsonian syndromes (PD and related disorders) from nondegenerative causes and potentially offer a "gold standard" for underlying neurodegeneration. Several studies have found abnormal scans in 0% to 55% of patients with clinically diagnosed DIP,[7] with most describing abnormalities in at least 10% to 20%. However, the clinical correlates of abnormal imaging have not been well described, and most of the studies focused on patients with schizophrenia who may have baseline striatal abnormalities. More

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than half of AP prescriptions in the U.S. Department of Veterans Affairs health system (VA) are for "off-label" indications,[8] offering the opportunity to study DIP outside the schizophrenic population. Here, we examine DAT-SPECT in a mixed cohort of psychiatric patients with DIP and report a strong association between abnormal olfaction and abnormal imaging, consistent with underlying neurodegeneration.

Patients and Methods

Subjects and Assessments

All study procedures were approved by the local institutional review board. We identified all patients who had undergone DAT-SPECT at our center between October 2012 and April 2016 using a Current Procedural Terminology code search. Manual chart review (J.F.M.) identified patients for whom DAT-SPECT was ordered to evaluate DIP. All subjects who underwent DAT-SPECT to evaluate DIP during this time frame were included in the analysis. During this time, 104 patients were evaluated at our center with DIP. DAT-SPECT was performed according to standard clinical protocol, whereby ^{123}I-ioflupane (185 MBq; DaTScan; GE Healthcare, Waukesha, WI) was intravenously administered. Images were acquired 3 hours postinjection with a dual-head Symbia gamma-camera (Siemens USA, Washington, DC). Scans were evaluated by a nuclear medicine physician and read as normal or abnormal according to clinical practice. Readers were unaware of clinical or olfactory status.

A standardized template was used to extract from the electronic medical record: demographics, psychiatric diagnosis and treatment, offending agent and dose (normalized using chlorpromazine equivalents, where possible), motor symptoms, objective olfactory testing (where available), and UPDRS motor scores (UPDRS-III), including subscores reflecting tremor, bradykinesia, rigidity, postural instability-gait difficulty (PIGD) items, or asymmetry. Olfactory function was assessed using the 40-item University of Pennsylvania Smell Test (UPSIT) or 12-item Brief Smell Identification Test (Sensonics, Inc., Haddon Heights, NJ). Raw scores were converted to age- and sex-specific percentiles based on normative data. Olfactory scores ≤10th percentile were considered abnormal, reflecting anosmia on the UPSIT in the age range studied. A more-stringent cutoff (<5th percentile) would result in reclassification of 1 subject (abnormal to normal) whereas less-stringent criteria (<20th percentile) would not change the classification of any subjects.

Statistical Analysis

Group differences between subjects with normal or abnormal DAT-SPECT were assessed using independent-sample *t* tests for continuous variables and chi-squared or Fisher's exact test for categorical variables (parametric and nonparametric methods yielded similar results). For significant associations in bivariate analysis, we performed binary logistic regression models with DAT-SPECT result as the dependent variable controlling for age, sex, or other covariates as described. Because of the small cohort size, only one covariate was included per model. All statistical tests were two-sided and significance was set at $P \leq 0.05$ using SPSS software (v20; IBM, Chicago, IL).

Results

We identified 33 DAT-SPECT scans performed at our center to evaluate DIP. The mean (standard deviation; SD) age of subjects was 63 (7.9) years and 29 (88%) were male. The suspected offending agents were: aripiprazole (33%), haloperidol or other first-generation agent (15%), olanzapine (15%), risperidone (15%), ziprasidone (6%), lurasidone (3%), valproic acid (3%), lithium (3%), or multiple agents (6%). The primary psychiatric diagnoses for which the offending agent was prescribed were: bipolar disorder (34%), chronic schizophrenia (24%), depression (15%), other psychoses (12%), and post-traumatic stress disorder (12%). Overall, seven (21%) of the scans were read as abnormal and consistent with a degenerative parkinsonian syndrome. A comparison of clinical features between subjects with normal and abnormal DAT-SPECT is shown in Table 1.

Subjects with normal and abnormal scans were similar in demographics except for a nonsignificant trend toward older age in those with abnormal DAT-SPECT. A total of 10 (30%) patients were smokers. The percentage of smokers was not significantly different based on DAT-SPECT result (Table 1), olfactory impairment ($P = 0.72$), or psychiatric diagnosis ($P = 0.43$). Motor features, including total UPDRS-3 score and subscores representing bradykinesia, rigidity, and asymmetry, did not differ between groups. There were trends toward less tremor and more-severe gait symptoms in subjects with abnormal scans, but these did not reach significance ($P = 0.09$ and $P = 0.10$, respectively). The distribution of psychiatric diagnoses and the proportion of subjects taking antidepressants that have a

TABLE 1 Comparison of demographic and clinical features in DIP patients with normal or abnormal DAT-SPECT

	DAT-SPECT Normal N = 26	DAT-SPECT Abnormal N = 7	*P* Value
Age, years	62 (8)	68 (8)	0.10
Sex, % male	89	86	1.0
Current smokers, %	34	14	0.40
UPDRS-III score	19 (10)	15 (5.0)	0.44
Bradykinesia	7.2 (6.1)	5.8 (5.5)	0.55
Tremor	4.7 (3.9)	1.8 (1.8)	0.09
Rigidity	3.4 (3.2)	4.5 (3.3)	0.45
PIGD	0.92 (0.69)	1.7 (1.9)	0.10
Asymmetry index	0.30 (0.33)	0.25 (0.25)	0.73
Psychosis, %	38	57	0.43
Dose, CPZ equivalents	2.5 (1.5)	1.0 (0.66)	0.004
DAT interfering drug, %	50	43	0.740
Olfactory percentile	44 (22)	13 (25)	0.005
Anosmia, % (N)	9 (2/23)	86 (6/7)	<0.001

Data are mean (SD) or percentages as noted. Psychosis refers to subjects with schizophrenia or other psychosis (most commonly schizoaffective disorder) as the psychiatric diagnosis. Group comparisons were assessed using independent-sample *t* tests for continuous variables and chi-squared or Fisher's exact test for categorical variables. Only 30 of 33 subjects had available results of objective olfactory testing.

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minor effect (<10%–15%) on DAT-SPECT[9] were similar between groups. However, intensity of treatment, represented by chlorpromazine equivalents, was significantly lower in the abnormal group (Table 1), and the association persisted in regression models controlling for age ($P = 0.04$) or psychiatric diagnosis ($P = 0.04$). Age- and sex-adjusted olfactory scores were significantly lower in subjects with abnormal DAT-SPECT. Anosmia was observed in only 9% of subjects with normal DAT-SPECT, but in 86% of subjects with abnormal scans. This association persisted in regression models adjusting for age or gender (odds ratio = 63; 95% confidence interval: 4.8–820; $P = 0.002$).

Discussion

DIP is a common differential diagnosis for PD and a better understanding of how to distinguish these entities is an unmet need, given that management and prognosis differs dramatically. In a cohort including many patients with diagnoses other than schizophrenia, we found that more than 1 in 5 subjects with suspected DIP had evidence of presynaptic dopaminergic denervation consistent with underlying degenerative parkinsonism.

Several previous studies have examined DAT-SPECT in patients with suspected DIP. One study retrospectively examined DAT-SPECT in subjects whose parkinsonism resolved after withdrawal of AP and found that up to 9% to 12% had abnormalities, suggesting that clinical outcome alone may be insensitive to underlying neurodegeneration.[10] Only one small study has prospectively examined DIP patients who have undergone DAT-SPECT, describing worsening motor function and L-dopa responsiveness indicative of PD in 8 of 9 cases with abnormal scans.[11] In the present study, overall motor severity, as well as asymmetry, were similar in subjects with normal and abnormal DAT-SPECT, although we may have been underpowered to detect small differences. Consistent with our previous observation that gait symptoms were worse in subjects with persistent DIP and greater tremor burden in subjects with DIP compared to PD,[12] we observed trends toward higher gait and lower tremor scores in subjects with abnormal SPECT, though these did not reach statistical significance. This may be attributable to lack of statistical power or a bias in the pattern of clinical characteristics (similar to PD) that motivated obtaining DAT-SPECT. These findings reinforce the idea that although group differences may be observed in comparing clinical features of DIP and PD, motor features are of little value to help differentiate the two on an individual basis.

Most psychiatric and neurologic characteristics were similar between subjects with normal and abnormal DAT-SPECT. However, chlorpromazine (CPZ) equivalents were lower, representing less dopaminergic blockade, in subjects with underlying dopaminergic denervation. One possibility is that lower intensity of therapy in subjects with abnormal DAT-SPECT reflected hypersensitivity to dopaminergic blockade attributed to subclinical nigrostriatal degeneration. Alternatively, differences in underlying psychiatric characteristics could explain less-intense treatment, but psychiatric diagnosis was not associated with DAT-SPECT result (Table 1) and the association persisted when adjusting for psychiatric diagnosis. Thus, dopamine blockers may act as a "stress test" for the nigrostriatal pathway by unmasking incipient PD. This may be an important clinical clue when parkinsonism emerges with relatively low AP doses —particularly of newer low-potency agents.

In contrast to the similarity of motor features between groups, we found that olfactory dysfunction, a common feature of PD that often predates motor symptoms, was associated with underlying dopaminergic denervation in suspected DIP (Table 1). A few studies have investigated olfaction as a biomarker in DIP. In one study of 59 AP-treated patients, 15 (25%) developed extrapyramidal symptoms and olfaction was worse in affected patients.[13] In another small study, 14 of 15 subjects with DIP had normal olfaction, but the 1 subject with anosmia had evidence of cardiac sympathetic denervation, another early nonmotor feature of PD.[14] Our results suggest that olfactory testing could be used on an individual basis to predict underlying dopaminergic denervation, consistent with PD or a related degenerative disorder, though the predictive value of normal olfaction may be better than for abnormal.

Our study has several limitations. The veteran cohort was largely male, whereas DIP is more common in women. Additionally, because of the population studied, approximately half of subjects were taking medications (primarily antidepressants) that could impact DAT binding by a small amount (10%–15%); however, this reduction does not influence routine clinical DAT-SPECT interpretation.[9] Furthermore, the proportion of subjects on potentially interfering drugs was similar in subjects with normal and abnormal imaging (Table 1), though this could be attributed to lack of statistical power. In this cross-sectional study, we were unable to assess clinical progression after DAT-SPECT to establish whether subjects ultimately met clinical criteria for PD or another degenerative disorder, such as dementia with Lewy bodies or MSA.

Olfactory testing in schizophrenic patients (approximately 25% of our cohort) presents challenges, including underlying olfactory abnormalities, cognitive or psychotic symptoms, and smoking history.[15] The issue of smoking is commonly raised in studies of olfaction, but the literature, in both schizophrenia[15] and healthy people, suggests a comparatively small impact of smoking on olfactory function, relative to factors such as age, sex, or the presence of underlying neurological disease (such as PD) that exert greater influence. Nonetheless, whereas normal olfaction in a schizophrenic patient with DIP may suggest a low risk of underlying PD, abnormal tests should be interpreted cautiously.

Olfactory testing is simple, inexpensive, and well established in the evaluation of parkinsonism. These results suggest that olfactory testing could guide empiric therapy in patients where DAT-SPECT is not feasible because of cost or availability. Additionally, these findings suggest that patients with DIP represent an "at-risk" cohort for underlying PD and that olfactory testing, together with DAT-SPECT, could be used in a stepwise screening approach for early or prodromal diagnosis, as has been done in the Parkinson's Associated Risk Study and

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others.[16] Future studies should focus on prospective longitudinal analysis of DIP subjects with abnormal olfaction and DAT-SPECT to characterize other clinical and molecular markers of PD that may lead to refined strategies for diagnosis and better understanding of the early events in disease progression.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

J.F.M.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
G.C.: 1B, 1C, 3B
J.G.D.: 1B, 3B
S.W.: 1C, 3B
J.R.W.: 1C, 3B
J.E.D.: 1A, 1B, 1C, 3B

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References

1. Barbosa MT, Caramelli P, Maia DP, et al. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambui study). *Mov Disord* 2006;21:800–808.
2. Aronson TA. Persistent drug-induced parkinsonism. *Biol Psychiatry* 1985;20:795–798.
3. Wilson JA, Primrose WR, Smith RG. Prognosis of drug-induced Parkinson's disease. *Lancet* 1987;1:443–444.
4. Lim TT, Ahmed A, Itin I, et al. Is 6 months of neuroleptic withdrawal sufficient to distinguish drug-induced parkinsonism from Parkinson's disease? *Int J Neurosci* 2013;123:170–174.
5. Rajput AH, Rozdilsky B, Hornykiewicz O, Shannak K, Lee T, Seeman P. Reversible drug-induced parkinsonism. Clinicopathologic study of two cases. *Arch Neurol* 1982;39:644–646.
6. Morley JF, Duda JE. Use of hyposmia and other non-motor symptoms to distinguish between drug-induced parkinsonism and Parkinson's disease. *J Parkinsons Dis* 2014;4:169–173.
7. Brigo F, Matinella A, Erro R, Tinazzi M. [^{123}I]FP-CIT SPECT (DaTSCAN) may be a useful tool to differentiate between Parkinson's disease and vascular or drug-induced parkinsonisms: a meta-analysis. *Eur J Neurol* 2014;21:1369–e90.
8. Leslie DL, Mohamed S, Rosenheck RA. Off-label use of antipsychotic medications in the department of Veterans Affairs health care system. *Psychiatr Serv* 2009;60:1175–1181.
9. Kagi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. *J Neurol Neurosurg Psychiatry* 2010;81:5–12.
10. Diaz-Corrales FJ, Sanz-Viedma S, Garcia-Solis D, Escobar-Delgado T, Mir P. Clinical features and 123I-FP-CIT SPECT imaging in drug-induced parkinsonism and Parkinson's disease. *Eur J Nucl Med Mol Imaging* 2010;37:556–564.
11. Tinazzi M, Antonini A, Bovi T, et al. Clinical and [123I]FP-CIT SPET imaging follow-up in patients with drug-induced parkinsonism. *J Neurol* 2009;256:910–915.
12. Hassin-Baer S, Sirota P, Korczyn AD, et al. Clinical characteristics of neuroleptic-induced parkinsonism. *J Neural Transm* 2001;108:1299–1308.
13. Kruger S, Haehner A, Thiem C, Hummel T. Neuroleptic-induced parkinsonism is associated with olfactory dysfunction. *J Neurol* 2008;255:1574–1579.
14. Lee PH, Yeo SH, Yong SW, Kim YJ. Odour identification test and its relation to cardiac 123I-metaiodobenzylguanidine in patients with drug induced parkinsonism. *J Neurol Neurosurg Psychiatry* 2007;78:1250–1252.
15. Moberg PJ, Agrin R, Gur RE, Gur RC, Turetsky BI, Doty RL. Olfactory dysfunction in schizophrenia: a qualitative and quantitative review. *Neuropsychopharmacology* 1999;21:325–340.
16. Jennings D, Siderowf A, Stern M, et al. Imaging prodromal Parkinson disease: the Parkinson Associated Risk Syndrome Study. *Neurology* 2014;83:1739–1746.

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