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Motor and non-motor features of Parkinson's disease that predict persistent drug-induced Parkinsonism

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ABSTRACT

Background: Drug-induced Parkinsonism is common, causes significant morbidity, and can be clinically indistinguishable from idiopathic Parkinson's disease. Additionally, drug-induced Parkinsonism may, in some cases, represent "unmasking" of incipient Parkinson's disease. Clinical features or tests that distinguish degenerative from pharmacologic Parkinsonism are needed.
Methods: We performed a retrospective case-control study of 97 drug-induced Parkinsonism subjects and 97 age-matched patients with Parkinson's disease. We compared the frequency of subjective motor and non-motor complaints, objective motor findings (Unified Parkinson's Disease Rating Scale Part III) and, where available, objective olfactory tests. We also performed a nested case-control study wherein we compared these same features between drug-induced Parkinsonism patients based on whether or not they recovered after changing the offending agent.
Results: Non-motor symptoms including constipation and sexual dysfunction were more common in Parkinson's disease than in drug-induced Parkinsonism. While total motor scores were similar between groups, Postural Instability-Gait Difficulty scores were also higher in Parkinson's disease. Features that were significantly different or showed a trend towards significance in both comparisons included subjective loss of facial expression, dream-enactment behavior, autonomic complaints and Postural Instability-Gait Difficulty scores. Hyposmia was more common in Parkinson's disease and was strongly predictive of persistent drug-induced Parkinsonism after therapy change (odds ratio 30.3, 95% confidence interval: 1.5–500, $p = 0.03$).
Conclusions: A constellation of motor and non-motor features may differentiate unmasked Parkinson's disease from drug-induced Parkinsonism. In particular, olfactory testing may offer a simple and inexpensive method to help predict outcomes in drug-induced Parkinsonism and, potentially, identify a cohort of pre-motor Parkinson's disease.

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1. Introduction

Parkinsonism is a clinical constellation including tremor, rigidity, bradykinesia and postural instability. While Parkinson's disease (PD) is the most common cause of Parkinsonism, a variety of neurodegenerative, structural, metabolic or toxic insults affecting the basal ganglia and nigrostriatal pathway may give rise to the clinical picture [1]. Among these, drug-induced Parkinsonism (DIP), most commonly associated with dopamine receptor blocking agents (DRBA) prescribed for psychotic disorders and depression, is a common cause of parkinsonian symptoms resulting in significant morbidity, treatment non-compliance, and disability [2].

DIP may sometimes represent "unmasking" of subclinical nigrostriatal dysfunction, such as incipient PD or another degenerative parkinsonian syndrome (e.g. Dementia with Lewy Bodies, Multiple System Atrophy) [3]. While cohort studies suggest that DIP is associated with less tremor, upper extremity predominance and more symmetric symptoms than PD, the presentations can be nearly identical [4,5]. Lack of a close temporal relationship between drug initiation and symptom onset, persistent symptoms after drug withdrawal or a robust response to levodopa can support a diagnosis of underlying PD. Conventional wisdom holds that Parkinsonism should resolve within a few weeks or months after DRBA

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withdrawal, but some patients recover only after a protracted period or not at all [6–8].

Parkinsonism can appear in the setting of chronic DRBA exposure, and concerns over worsening psychiatric symptoms in patients being treated for psychotic disorders often make empiric interventions unattractive or risky. Thus, while a diagnosis of DIP is sometimes straightforward, it often may be difficult or impossible to exclude underlying PD and initiate appropriate management. DIP has been described as the second most common cause of Parkinsonism after PD in population-based epidemiologic studies [9,10], highlighting the frequency with which clinicians must face this challenging differential diagnosis.

If DIP represents unmasking of underlying neurodegeneration, one would expect overlap between clinical features (beyond motor symptoms) of PD. Because DIP subjects, by definition, lack parkinsonian motor signs prior to treatment with the offending agent, the shared features would likely be those present prior to motor symptoms in PD. Degenerative changes in PD are associated with a number of non-motor symptoms (NMS) including olfactory, sleep, mood, cognitive and autonomic disturbances, some of which can manifest many years before motor symptoms [11–13]. In order to identify symptoms or clinical features that distinguish drug-induced from degenerative Parkinsonism and might be used to predict clinical outcomes, we conducted a retrospective case-control study of patients diagnosed with DIP or PD, with a particular focus on NMS, and then compared these features in DIP subjects based on their recovery after change of the offending agent.

2. Methods

2.1. Subjects

We identified subjects diagnosed with DIP at the Philadelphia Veterans Affairs Medical Center's (PVAMC) Parkinson's Disease Research Education and Clinical Center (PADRECC) using a database search with ICD9 code 332.1 (secondary Parkinsonism). This code identifies subjects with not only DIP but also other secondary etiologies (most commonly vascular Parkinsonism). Charts were then manually reviewed by a movement disorder neurologist (JFM) to identify subjects where the clinical diagnosis of the treating movement disorder neurologist was DIP and no other secondary etiology was suspected. The charts were then further reviewed to confirm that subjects developed parkinsonism (resting tremor, rigidity, bradykinesia and/or postural instability) only after treatment for at least 6 weeks with a drug having known dopamine-receptor blocking activity or that had been previously associated with DIP. This strategy included DIP subjects only in whom there was agreement between two movement disorder neurologists about the diagnosis based on timing and clinical phenomenology.

A total of 97 DIP subjects were identified. A group of 97 age-matched PD subjects was identified with a similar strategy using ICD9 code 332.0 (paralysis agitans) and a chart review to confirm the diagnosis. Subjects for whom a PADRECC intake questionnaire could not be identified (see below) were excluded from the analysis.

2.2. Data acquisition and analysis

A standardized template was used to extract demographics, details of psychiatric diagnosis and treatment, duration of motor symptoms, objective olfactory testing (where available), and Unified Parkinson's Disease Rating Scale [14] motor scores (UPDRS-III) and subscores reflecting tremor, bradykinesia, rigidity, postural instability-gait difficulty (PIGD) items or asymmetry from the electronic medical record of initial and follow-up visits. Unified Parkinson's Disease Rating Scale part 1 and 2 responses, Schwab & England Activities of Daily Living Scale, together with subjective patient reports (queried as yes/no for each symptom) of motor complaints and NMS, were recorded from the standardized PADRECC intake questionnaire filled out by patients at their initial visit. Subjects for whom a completed questionnaire could not be identified were excluded. In cases where it had been performed, results of objective olfactory testing (University of Pennsylvania Smell Identification Test (UPSIT [15],), Brief Smell Identification Test version B (BSIT [16],) or Pocket Smell Test (PST, www.sensonics.com)) were recorded as normal or abnormal (<25th percentile for age/gender for UPSIT and BSIT, one or more items incorrect for PST).

Clinical outcomes in DIP were acquired separately from potential predictors by independent research personnel. Recovery was defined by 50% decrease in UPDRS motor score or clear statement of recovery by the treating physician. The first definitive followup where recovery could be assessed occurred between 3 and 6 months for 32 (86%) of subjects. Only 3 (%) of subjects had initial followup at > 1 year. For the analyses reported here, recovery was assessed at the first followup after 3 months of recovery. Classification of recovery changed in only 1 subject if assessed at >1 year (a patient who initially improved but went on to develop levodopa-responsive PD after 3 years of follow-up). Additionally, using 1 year as the standard for recovery would have eliminated 14 (38%) subjects due to insufficient followup.

Group differences comparing DIP to PD or reversible DIP (rDIP) to persistent DIP (pDIP) were assessed using chi-squared tests (Fisher's exact test when any outcome was experience by < 5 subjects) for proportions or *t*-tests for continuous variables. All statistical tests were two sided and significance was set at $p \leq 0.05$. A trend towards significance was defined as $p \leq 0.15$. This study was approved by the PVAMC Institutional Review Board.

3. Results

3.1. Features that distinguish DIP from PD

The first stage of this study examined 97 clinically diagnosed DIP patients with a mean age of 64 ± 10 (range: 44–89). Of these, 92 (95%) were male. The suspected offending agents (number of subjects) at the time of initial evaluation were risperidone (34), olanzapine (15), haloperidol (10), ariprazole (6), ziprasidone (5), metoclopramide (4), thioridazine (2), lithium (1), perphenazine (1), fluphenazine (1), and trifuoperazine (1). Seventeen subjects were taking multiple potentially offending drugs. Comparisons of demographic characteristics, UPDRS section scores and Schwab and England activities of daily living scale between the DIP subjects and an age-matched group of PD are shown in Table 1. Not surprisingly, UPDRS Section 1 scores (which query mood and thought disturbances), were higher in DIP than in PD. Demographics, aggregate UPDRS Section 2 (subjective motor impairment), Section 3 (motor exam) and ADL scores were similar between the groups ($p > 0.05$). Comparison of patient-endorsed motor symptoms (including tremor, stiffness, slowness, walking problems, Table 2) in DIP subjects versus PD subjects revealed that while the frequency of most complaints was similar between the groups, subjects with PD more often endorsed "loss of facial expression" (43% vs. 28%, $p = 0.05$, Table 2).

We compared objective motor findings between DIP and PD subjects based on UPDRS-III total motor score and subscales encompassing specific motor domains (tremor, rigidity, bradykinesia, postural instability/gait disorder-PIGD, Table 3). PD subjects had significantly more motor asymmetry and a trend towards lower tremor scores ($p = 0.08$) than DIP subjects (Table 3). Additionally, in our cohort, PIGD scores were more than two-fold higher in PD compared to DIP (3.7 ± 0.3 vs. 1.7 ± 1.6, $p < 0.001$; Table 3). PIGD phenotypes have been linked with increasing disease duration in PD. To address whether disease duration confounded our finding that PIGD scores are a distinguishing feature, we dichotomized the PD cohort at the median disease duration (3 years or less vs. 4 years or more) and found that the PIGD scores were

Table 1
Demographic and disease characteristics of cohort and comparison groups. Data are mean (standard deviation) unless otherwise indicated. pDIP, persistent DIP. rDIP, reversible DIP.

	PD vs. DIP			Persistent DIP vs. reversible DIP		
	PD $N = 97$	DIP $N = 97$	*P*	pDIP $N = 15$	rDIP $N = 22$	*p*
Age	65 (6.8)	64 (10)	0.58	69 (11)	63 (10)	0.10
Gender (% male)	99	95	0.11	100	93	0.41
Smokers (%)	17	21	0.63	27	19	0.66
UPDRS-I	3.5 (2.9)	5.6 (3.7)	0.002	2.8 (2.5)	4.3 (4.3)	0.44
UPDRS-II	13 (8.9)	13 (8.5)	0.81	11 (10)	7.4 (6.3)	0.25
Schwab & England	76 (20)	70 (25)	0.13	70 (23)	80 (21)	0.27