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ORIGINAL ARTICLE

Clinical Features Indicating Nigrostriatal Dopaminergic Degeneration in Drug-Induced Parkinsonism

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ABSTRACT

Objective Patients with drug-induced parkinsonism (DIP) may have nigrostriatal dopaminergic degeneration. We studied the clinical features that may indicate nigrostriatal dopaminergic degeneration in patients with DIP.

Methods Forty-one DIP patients were classified into normal and abnormal [^{18}F] FP-CIT scan groups. Differences in 32 clinical features and drug withdrawal effects were studied.

Results Twenty-eight patients had normal (Group I) and 13 patients had abnormal (Group II) scans. Eight patients of Group I, but none of Group II, had taken calcium channel blockers (p = 0.040). Three patients of Group I and six of Group II had hyposmia (p = 0.018). After drug withdrawal, Group I showed greater improvement in Unified Parkinson's Disease Rating Scale total motor scores and subscores for bradykinesia and tremors than Group II. Only hyposmia was an independent factor associated with abnormal scans, but it had suboptimal sensitivity.

Conclusion None of the clinical features were practical indicators of nigrostriatal dopaminergic degeneration in patients with DIP.

Key Words Drug-induced parkinsonism; dopamine transporter; positron-emission tomography; hyposmia.

Nigrostriatal dopaminergic degeneration is found in 30 to 75% of patients clinically diagnosed with drug-induced parkinsonism (DIP).[1-4] Dopamine transporter (DAT) single photon emission computed tomography (SPECT) and photon emission tomography (PET) studies of DIP showed that patients with normal scans have dopa-resistant parkinsonism that may not progress even if the offending drug treatment is continued. Conversely, patients with reduced striatal uptake have dopa-responsive parkinsonism that may deteriorate even after drug withdrawal.[3-6] Thus, clinical features must be defined to help differentiate DIP patients with normal and abnormal scans. DAT imaging evaluates the striatal presynaptic dopaminergic function and is useful for the differential diagnosis of parkinsonism and the assessment of severity and progression.[7,8] Additionally, [^{18}F] N-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) is superior to SPECT because of its better spatial resolution.[8]

Three DAT SPECT studies from the same group reported that compared to DIP patients with normal scans, those with abnormal scans were older, more frequently had asymmetric and severe parkinsonism, and less frequently had bucco-linguo-masticatory (BLM) dyskinesia.[2,4,9] One DAT PET study also showed that DIP patients with normal scans had more frequent symmetric parkinsonism compared to abnormal ones.[10] Conversely, four other SPECT studies did not find differences in clinical features between patients with normal and abnormal scans.[1,5,11,12]

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However, those four studies included only 13 to 22 patients with DIP.

In 41 patients with DIP, we studied demographic and clinical parameters that may differentiate DIP patients with normal and abnormal [^{18}F] FP-CIT PET scans. In 31 of the 41 patients, we studied whether DIP patients with normal and abnormal scans could be differentiated by changes in Unified Parkinson's Disease Rating Scale (UPDRS) scores after drug withdrawal.

MATERIALS & METHODS

Patients

We reviewed the medical records of 41 DIP patients who underwent brain MRI and DAT PET studies. DIP was diagnosed according to parameters described in a previous report: the presence of two or more cardinal symptoms of parkinsonism, no history of parkinsonism before use of the offending drug and onset of parkinsonism symptoms during use of the offending drug.[13] Patients were excluded if they had signs compatible with atypical parkinsonism and other causes of secondary parkinsonism. In 31 of the 41 patients, we evaluated changes in parkinsonian motor deficits after withdrawal of the offending drug. The present study was approved by the Institutional Review Board of the Gangnam Severance Hospital, Yonsei University College of Medicine (IRB # 3-2016-0018).

Methods

We recorded the demographics, duration of parkinsonism, family history of parkinsonism, smoking history, and offending drug histories. We collected data about falls, aspiration, dysarthria, and BLM dyskinesia. We registered initial parkinsonian symptoms including asymmetry. We collected data on non-motor symptoms and Mini-Mental State Examination (MMSE) scores.

We measured UPDRS motor scores and counted patients who presented with asymmetric parkinsonian motor deficits ($\geq$ 4 side to side difference in UPDRS motor score).[9] We also computed indexes of asymmetric parkinsonian motor deficits (sum of UPDRS motor scores of the more affected side divided by that of the less affected side) and disproportionate arm involvement (sum of UPDRS motor scores of the arms divided by that of the legs). In 31 of 41 patients, changes in UPDRS total motor scores and subscores for bradykinesia, rigidity, tremors, and axial motor deficits were measured after withdrawal of the drug for at least 2 months.

Quantitative measurements of PET images were performed as reported previously by our study group.[14] We considered a scan as abnormal when the mean bilateral putamen DAT uptake was reduced more than two standard deviations from that of 36 age-matched healthy controls who had no history of neurological illness and no abnormal signs on neurological examination. We classified patients into normal and abnormal scan groups.

Statistics

Using chi-square tests (Fisher's exact tests) for categorical variables and independent two sample *t*-tests for continuous variables, we examined the group differences for all the parameters. For the parameters with significant group differences, we performed univariate and multivariate backward binary logistic regression analyses controlled for age and sex to identify independent factors in distinguishing DIP with normal and abnormal scans. For the use of calcium channel blockers (CCBs), exact binary logistic regression analysis was performed using Statistical Analysis System software (SAS version 9.1; SAS Inc., Cary, NC, USA). All other statistical analyses were performed using SPSS (version 23.0; SPSS Inc., Chicago, IL, USA). The results were considered statistically significant when the *p*-value was < 0.05.

RESULTS

Twenty-eight patients (Group I; 68.3%) had normal scans and 13 (Group II; 31.7%) had abnormal scans. The mean age at onset was similar between Group I and II. Women were more prevalent than men in both groups. There was no significant group difference in female predominance. The means of the duration of parkinsonism were not significantly different (Table 1).

In both groups, common causative drugs were antiemetics and antidepressants. Eight patients of Group I, but none of Group II, had taken CCBs ($p = 0.040$). Multiple drug therapy was common in both groups (Supplementary Table 1 in the only online Data Supplement). The duration of exposure to drugs for Group I was longer than Group II, but the difference

was not significant (Table 1).

The frequencies of various non-motor deficits were not significantly different between groups. However, compared to Group I, Group II patients had more frequent hyposmia (p = 0.018). There was no significant group difference in the mean MMSE scores or the frequency of dementia (MMSE score ≤ 24) (Table 2).

Compared to Group I, Group II patients more often had a history of falls, aspiration, and dysarthria, but the differences were not significant. BLM dyskinesia was uncommon in both groups. In both groups, tremors and gait disturbances were common initial symptoms. There was no significant difference in the frequency of asymmetric onset (Table 2).

The means of UPDRS total motor scores of Group I and II were similar. In addition, there were no significant differences in subscores for bradykinesia, rigidity, tremor or axial motor impairments. Four patients (14.3%) of Group I and three patients (23.1%) of Group II had asymmetric parkinsonism. There were no significant differences in the UPDRS indexes of asymmetry or disproportionate upper-to-lower involvement of the extremities (Supplementary Table 2 in the only online Data Supplement).

In 31 patients (Group I = 20 patients; Group II = 11 patients), changes in UPDRS scores were measured after a mean of 4.03 months of drug withdrawal. Compared to Group II, Group I showed greater reductions in UPDRS total motor scores (-8.75 ± 9.16 vs. 0.18 ± 7.76; p = 0.011) and subscores for bradykinesia (p = 0.029), total tremors (p = 0.019), and resting tremors (p = 0.021). However, there were no differences in residual parkinsonian motor deficits and changes in the indexes of asymmetry or disproportionate upper-to-lower involvement of the extremities (Supplementary Table 2 in the only online Data Supplement).

Univariate regression analyses showed that the frequency of hyposmia (p = 0.017) and greater reductions in total motor scores (p = 0.040) and subscores for bradykinesia (p = 0.047) after drug withdrawal were associated with abnormal scans (Supplementary Table 3 in the only online Data Supplement). Using multivariate regression analysis, only the frequency of hyposmia was an independent factor associated with abnormal scans (p = 0.030) (Supplementary Table 3 in the only online Data Supplement). Hyposmia had relatively high specificity (89.3%) and negative predictive value (78.1%) but had low sensitivity (46.2%) and positive predictive value (66.7%) for abnormal scans.

DISCUSSION

In the present study, we performed a systematic analysis of 32 clinical parameters between patients with normal and abnormal DAT scans. Compared to DIP patients with normal scans, those with abnormal scans had more frequent hyposmia. No pa-

Table 1. Demographics and clinical characteristics of 41 patients with drug-induced parkinsonism with normal and reduced putamen FP-CIT uptake

	Group I (n = 28)	Group II (n = 13)	p value
Age at onset (yrs)	71.29 ± 9.34	67.38 ± 8.88	0.214
Age at examination (yrs)	72.72 ± 9.68	68.46 ± 8.84	0.187
Gender (male: female)	5:23 (82.1)	5:8 (61.5)	0.241
Duration of drug exposure (mo)*	4.66 ± 3.79	3.04 ± 2.96	0.182
Duration of parkinsonism (mo)†	14.16 ± 14.54	15.54 ± 15.44	0.783
Family history of parkinsonism	2 (7.1)	1 (7.7)	> 0.999
Smoking history	1 (3.6)	2 (15.4)	0.232

Group I: normal putamen FP-CIT uptake, Group II: reduced putamen FP-CIT uptake. Mean ± standard deviation, numbers in parentheses = %. *duration of drug exposure prior to symptom onset (mo), †duration of parkinsonism before diagnosis (mo).

Table 2. Comparisons of non-motor and motor deficits between 41 drug-induced parkinsonism patients with normal and reduced putamen FP-CIT uptake

	Group I (n = 28)	Group II (n = 13)	p value
Non-motor deficits			
RBD	3 (10.7)	4 (30.8)	0.181
Hyposmia	3 (10.7)	6 (46.2)	0.018*
Urinary symptom	4 (14.3)	5 (38.5)	0.113
Urgency	3 (10.7)	3 (23.1)	0.361
Urge incontinence	3 (10.7)	5 (38.5)	0.084
Postural dizziness	11 (39.3)	8 (61.5)	0.313
Erectile dysfunction	2/5 (40.0)	4/5 (80.0)	0.524
Constipation	15 (53.6)	7 (53.8)	0.987
MMSE	23.39 ± 1.92	24.46 ± 5.35	0.555
Dementia (MMSE ≤ 24)	9 (39.1)	4 (30.8)	0.727
Motor deficits			
Falls	7 (25.0)	5 (38.5)	0.469
Aspiration	2 (7.1)	2 (15.4)	0.579
Dysarthria	10 (35.7)	5 (38.5)	> 0.999
BLM dyskinesia	5 (17.9)	1 (7.7)	0.645
Initial symptoms			0.271
Tremors	13 (46.4)	3 (23.1)	
Gait disturbance	6 (21.4)	7 (53.8)	
Bradykinesia	5 (17.9)	2 (15.4)	
Dysarthria	2 (7.1)	1 (7.7)	
Dyskinesia	2 (7.1)	0 (0)	
Asymmetric onset	9 (32.1)	5 (38.5)	0.734

Group I: normal putamen FP-CIT uptake, Group II: reduced putamen FP-CIT uptake. Mean ± standard deviation, numbers in parentheses = %. *p-value < 0.05. RBD: rapid eye movement sleep behavior disorder, MMSE: Mini-Mental Status Examination, BLM: bucco-linguo-masticatory.

tients with reduced putamen DAT uptake had been exposed to CCBs. They showed deterioration or less improvement in UPDRS total motor scores and subscores for bradykinesia and tremors after drug withdrawal. However, only hyposmia was associated independently with abnormal scans at baseline.

A DAT SPECT study reported that DIP patients with abnormal scans were significantly older than those with normal scans.[9] However, the present study and other studies have shown no significant difference in age of onset.[1-4,10,15]

An Italian group reported no female predominance in DIP patients with normal and reduced striatal DAT uptake.[4,9] However, two other studies from the same group and the present study found similar female predominance in DIP patients with normal and abnormal scans.[2,3] These findings suggest the high vulnerability of females to DIP, even in females with reduced nigrostriatal dopaminergic innervation.[16]

An FP-CIT PET study reported lower symmetric frequency of parkinsonism in the abnormal scan than the normal scan.[10] However, the present study showed no significant difference in asymmetric parkinsonism as measured by frequency, UPDRS score and asymmetry index. The previous study also showed that the interval from drug intake to the onset of parkinsonian symptoms was longer in patients with an abnormal scan than a normal scan. However, the present study showed no significant difference between the two groups.

The drug exposure period before the onset of parkinsonism was longer in patients treated with CCBs than those treated with dopamine blockers.[17] Tremor was the main symptom induced by CCBs, whereas rigidity was the most common feature induced by other offending drugs.[17] In the present study, eight patients with normal scans had taken CCBs, while none with abnormal scans had taken CCBs (p = 0.040). Although the difference was not significant using regression analyses, large studies are needed to determine whether CCBs can rarely uncover subclinical nigrostriatal dopaminergic degeneration.

A DAT SPECT study of DIP reported that patients with abnormal scans had abnormal odor threshold, discrimination and identification, while patients with normal scans had abnormal odor threshold.[18] In the present study, 46% of patients with abnormal scans reported hyposmia compared to 11% of those with normal scans. Although a history of hyposmia was an independent factor, its suboptimal sensitivity for the detection of abnormal scans in DIP limits its use in clinical practice.

In the present study, 39% of patients with abnormal scans had urge incontinence. Their mean duration of parkinsonism was only one year. Postmortem pathological studies are needed to define how many of these patients have multiple system atrophy.

A DAT SPECT study of DIP reported that BLM dyskinesia is more frequent in patients with normal scans than in those with abnormal scans. Most patients included in that study had schizophrenia and were being treated with neuroleptics.[2] The present study of patients with different illnesses treated using a variety of drugs did not show differences in the frequency of BLM dyskinesia.[15]

No previous dopaminergic brain imaging studies compared differences in the initial symptoms of DIP patients with normal and abnormal scans. Only one PET study compared the frequency of tremors at rest and orolingual dyskinesia.[10] However, they did not compare other initial symptoms. In the present study, the most common initial symptoms were tremors in patients with normal scans and gait disturbances in patients with abnormal scans. However, there were no significant group differences in the frequencies of initial symptoms, including asymmetric onset.

Two SPECT studies and one PET study reported that DIP patients with abnormal scans had more severe and asymmetric parkinsonism.[2,4,10] However, in the present study, patients with abnormal scans had no significant differences in UPDRS motor scores nor the frequencies and severities of asymmetric parkinsonism.[1,9] The present study also showed no significant group differences in UPDRS subscores for axial motor deficits and indexes for disproportionate upper-to-lower involvement of the extremities.

Complete recovery after drug withdrawal has been considered an indicator of normal nigrostriatal dopaminergic function in patients with DIP.[15,19] In the present study, none of the UPDRS changes independently indicated an abnormal scan. In addition, patients with normal and abnormal scans showed a similar degree of residual parkinsonian motor deficits.

In conclusion, among 32 baseline clinical parameters and changes in UPDRS scores after drug with-

drawal, only hyposmia was independently associated with nigrostriatal dopaminergic degeneration in patients with DIP. However, hyposmia does not appear to be a practical indicator of abnormal scans. Dopaminergic functional imaging studies are needed to detect nigrostriatal degeneration in patients clinically diagnosed with DIP.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.16045.

Conflicts of Interest

The authors have no financial conflicts of interest.

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