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LETTER TO THE EDITOR

Factors Associated With Anticholinergic-Induced Oral-Buccal-Lingual Dyskinesia in Parkinson's Disease

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Dear Editor,

Anticholinergics are often used to control tremor in patients with Parkinson's disease (PD), but rare cases of involuntary oral-buccal-lingual dyskinesia may develop in patients with PD during anticholinergic treatment.[1-4] This dyskinesia differs from levodopa-induced dyskinesia (LID): anticholinergic-induced dyskinesia (AID) affects the orofacial area and lasts throughout the waking hours, while LID typically affects the trunk or limbs, and its presence fluctuates depending on the pharmacokinetics of the dopaminergic drugs.

We collected medical data from three university hospitals and analyzed them to identify the factors related to the development of AID. The detailed methods and procedures of patient selection are presented in the Supplementary Material and Supplementary Figure 1 in the online-only Data Supplement.

Among the 1429 patients with PD who were identified through screening of medical records, 247 patients (17.3%) underwent anticholinergic therapy. After applying the inclusion and exclusion criteria, 13 patients with AID and 164 patients without AID were selected. The clinical characteristics and medication data of the two patient groups are shown in Table 1, and detailed clinical data of the 13 patients with dyskinesia are provided in Supplementary Table 1 in the online-only Data Supplement. The age of onset of PD was higher in patients with AID than in those without AID (70.7 vs. 60.7 years). Patients with AID showed significantly milder symptoms, as assessed with the Unified PD Rating Scale (UPDRS) motor score (18.3 vs. 25.4) and its subscores for bradykinesia (7.1 vs. 9.8) and rigidity (4.3 vs. 6.4), compared to those without AID. In terms of anticholinergic therapy, patients with AID were also older at the initiation of anticholinergic therapy than those without AID (72.8 vs. 63.8 years). The duration of PD prior to the initiation of anticholinergic therapy was shorter in patients with AID than in those without AID (25.1 vs. 37.4 months).

Detailed data on medication use at the initiation of anticholinergic therapy and at follow-up are presented in Supplementary Table 2 in the online-only Data Supplement. The levodopa and levodopa-equivalent daily doses (LEDDs) of patients with AID did not differ from those of patients without AID, but changes in the levodopa daily dosage and LEDD between initiation and follow-up were significantly lower in patients with AID than in those without AID.

A logistic regression model including factors that significantly differed between the two patient groups revealed that older age at onset of PD (B = 0.135; odds ratio = 1.145; 95% confidential interval, 1.044–1.255; p = 0.004) and a lower UPDRS motor score (B = -0.093; odds ratio = 0.911; 95% confidential interval, 0.835–0.994; p = 0.036) were associated with the occurrence of AID.

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Table 1. Clinical characteristics and medication data of patients with and without anticholinergic-induced dyskinesia

Variable	With dyskinesia (*n* = 13)	Without dyskinesia (*n* = 145)	*p*
Sex, male	5 (38.5)	73 (50.3)	0.412
Age at onset of PD, yr	70.7 ± 6.3	60.7 ± 9.7	< 0.001
UPDRS motor score*	18.3 ± 4.8	25.4 ± 11.5	0.001
Tremor	2.7 ± 2.3	4.3 ± 3.3	0.092
Bradykinesia	7.1 ± 3.1	9.8 ± 5.4	0.021
Rigidity	4.3 ± 2.3	6.4 ± 3.9	0.013
Posture/gait	1.8 ± 1.6	2.2 ± 1.9	0.464
Hoehn & Yahr stage*	2.0 ± 0.5	2.0 ± 0.6	0.862
Motor subtype*			0.832
Tremor dominant	5 (41.7)	37 (44.0)	
Mixed	2 (16.7)	9 (10.7)	
PIGD	5 (41.7)	38 (45.2)	
Age at initiation of AC, yr	72.8 ± 6.0	63.8 ± 9.3	0.001
Time from PD onset to ACs, month	25.1 ± 13.4	37.4 ± 34.0	0.013
Time from any drug to ACs, month	12.3 ± 11.6	16.7 ± 27.2	0.559
ACs			0.770
Benztropine	3 (23.1)	41 (28.3)	
Procyclidine	7 (53.8)	63 (43.4)	
Trihexyphenidyl	3 (23.1)	41 (28.3)	
AC dose, mg/day			
Benztropine	1.67 ± 0.58	1.98 ± 0.88	0.555
Procyclidine	6.43 ± 1.34	6.87 ± 2.29	0.623
Trihexyphenidyl	2.33 ± 1.53	3.15 ± 2.58	0.596

Values are presented as mean ± standard deviation or *n* (%).
*data were available for 12 of 13 patients with dyskinesia and 84 of 145 patients without dyskinesia.
PD, Parkinson's disease; UPDRS, Unified PD Rating Scale; PIGD, postural instability and gait disturbance; AC, anticholinergic.

These factors associated with AID are quite different from those associated with LID. For LID, younger age at onset of PD and more severe motor symptoms of PD are well established as important risk factors.[5] Since patients with a younger onset of PD also show relatively severe dopaminergic neuron loss, both risk factors for LID are related to severe dopaminergic neuron loss. Therefore, the present findings suggest that the pathophysiology of AID differs from that of LID and is related to less impairment of dopaminergic activity.

Interestingly, old age is a risk factor for tardive dyskinesia (TD), which shares an oral-buccal-lingual location and choreiform phenomenology with AID. TD also has a significant relationship with AID: schizophrenic patients with TD were more likely to have received anticholinergics than those without TD, and anticholinergics worsened existing TD. Two reports, including a placebo-controlled double-blind study,[6] demonstrated that discontinuing anticholinergics improved TD symptoms and that restarting anticholinergics aggravated TD symptoms. These findings imply that anticholinergics have synergistic or additive effects on TD. Although the pathophysiology of TD remains poorly understood and there are diverse hypotheses that may explain this ambiguity, TD has been conceptualized as resulting from a dopaminergic/cholinergic imbalance in the basal ganglia.[6,7] According to this imbalance concept, TD indicates the relative predominance of the dopaminergic system; therefore, the suppression of central cholinergic activity by anticholinergics can worsen the imbalance and further aggravate dyskinesia. In the same context, anticholinergic agents in patients with PD may increase dopaminergic activity and lead to dyskinesia. Since dopaminergic activity is impaired in patients with PD, exogenous dopaminergic replacement seems essential to the development of AID. All the patients with available medication information,[3,4] including our cases, were treated with levodopa and anticholinergics. Moreover, Hauser and Olanow[3] reported that the discontinuation of levodopa improved AID in a patient who was treated with levodopa and anticholinergics. Thus, a higher dose of dopaminergic drugs or milder motor symptoms may be associated with AID, which is consistent with the present results showing milder symptoms in patients with AID.

There are several limitations of this study. First, anticholinergics are typically prescribed in selected patients, which might lead to divergence of the data from that of the general PD population in terms of symptomatology and demographic characteristics. Second, although this is the largest dataset of PD patients with AID to date, the number of subjects was relatively small, and more data are needed to draw concrete conclusions. Third, there can be a lack of clarity in the diagnosis of AID. We carefully chose the criteria to identify AID; however, all the other diagnoses, such as TD, spontaneous dyskinesia, and dyskinesia induced by another drug, could not be completely ruled out. In particular, use of anticholinergics might lead to voluntary movement due to dryness of mouth or other discomfort in the oral cavity. To rule out this "pseudodykinetic" movement, we selected only patients with clear documentation of the involuntary nature of the movement. Finally, anticholinergics were not readministered due to ethical concerns or patient refusal except for in one patient. However, the readministration of anticholinergics may not have improved the specificity of the diagnosis.

In conclusion, older age at onset of PD and milder motor symptoms are risk factors for the development of AID, suggesting that the pathophysiologic basis of AID might be different from that of LID.

Ethics Statement

This study was approved for human experiment from the Institutional Review Board (IRB) of the Yonsei University Wonju Severance Christian Hospital (approval number: CR320154), and the study was conducted according to the Declaration of Helsinki. Obtaining informed consent was exempted by

the IRB and local regulation due to the retrospective design.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.23069.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

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