Presynaptic dopamine depletion predicts levodopa-induced dyskinesia in de novo patients with Parkinson's disease

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ABSTRACT

Presynaptic dopamine depletion predicts levodopa-induced dyskinesia in de novo patients with Parkinson's disease

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Although presynaptic dopamine depletion has been considered essential for the development of levodopa-induced dyskinesia (LID) in patients with Parkinson's disease (PD), this association has been difficult to demonstrate. It was investigated whether the magnitude of presynaptic dopamine depletion is a risk factor for the development of LID in this study by quantitatively analyzing ^{18}F-FP-CIT positron emission tomography (PET) data. This retrospective cohort study enrolled a total of 127 drug-naïve de novo patients with PD who completed ^{18}F-FP-CIT PET scanning at their initial evaluation. The patients visited our outpatient clinic every 3–6 months and had been followed for a minimum of 2 years since beginning dopaminergic medication. The predictive

power of the ^{18}F-FP-CIT uptake of striatal subregions and other clinical factors for the development of LID was evaluated using Cox proportional hazard models. During a mean follow-up period of 3.4 years, 35 patients with PD (27.6%) developed LID. Patients with LID showed less dopamine transporter (DAT) activity in the putamen than did those without LID. Multivariate Cox proportional hazard models revealed that the DAT uptakes of the anterior, posterior, and whole putamen were significant predictors of the development of LID, whereas DAT activity in the caudate and ventral striatum were not significantly correlated with the development of LID. Additionally, younger age at onset of PD and higher dose of levodopa were also significant predictors of LID. The present results provide convincing evidence that presynaptic dopaminergic denervation plays a crucial role in the development of LID.

Key words : levodopa, dyskinesia, Parkinson's disease, presynaptic, FP-CIT, PET

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I. INTRODUCTION

Levodopa-induced dyskinesia (LID) is one of the most disabling complications in patients with Parkinson disease (PD) who are treated chronically with levodopa. Observational studies have reported that about 60% of PD patients treated with levodopa for 5 years had experienced LID,[1,2] and randomized clinical trials have also shown that LID developed in approximately half of PD patients after 4 years of levodopa treatment.[3-5]

In terms of risk factors, the development of LID is closely associated with higher dose of levodopa,[1,6] longer duration of levodopa treatment,[7] and younger age at onset of PD.[2,8] Additionally, lower body weight,[9] female sex,[10] and

genetic susceptibility[11] have also been suggested as contributors to increase risk for LID. Although the mechanism for LID is not completely understood, presynaptic dopaminergic denervation has been considered essential for its development, along with chronic pulsatile stimulation of dopamine receptors.[12] Importantly, animal studies have indicated that nigrostriatal damage is a prerequisite for LID induction and that the magnitude of nigrostriatal dopaminergic denervation is closely associated with the development of LID.[13-15] However, recent clinical studies have failed to show association between the severity of motor symptoms and development of LID.[1,2,7,16] The results of functional neuroimaging analyses have also been inconsistent; some cross-sectional studies using positron emission tomography (PET) reported that the degree of synaptic dopaminergic denervation was associated with motor fluctuation in patients with PD, [17-19] however, these studies had small sample sizes[17,19] or showed significant differences in terms of disease duration at baseline or age of onset.[18] Furthermore, one study observed similar degrees of presynaptic dopaminergic denervation in patients with and without LID.[20] Therefore, the present study evaluated the association between presynaptic dopaminergic depletion and LID by quantitatively analyzing ^{18}F-FP-CIT PET data to determine whether the magnitude of dopamine depletion may act as a risk factor for the development of LID in de novo patients with PD.

II. MATERIALS AND METHODS

1. Subjects

This retrospective cohort study enrolled a total of 132 patients with PD recruited from a university hospital. The subjects were drug-naïve de novo PD patients who completed an ^{18}F-FP-CIT PET scan at the time of PD diagnosis, which was performed according to the clinical criteria of the UK PD brain bank.[21] The inclusion criteria were decreased dopamine transporter (DAT) uptake in the putamen and a minimum follow-up period of 2 years since beginning dopaminergic medication. Patients who had focal lesions or lacunar infarction in the basal ganglia according to magnetic resonance imaging were excluded from the study. All patients had visited our outpatient clinic every 3–6 months, and two movement disorder experts (Y.H.S., P.H.L.) assessed the presence of LID based on either history or direct neurological examination at every visit. During follow-up, two patients were diagnosed with dementia with Lewy body and multiple system atrophy, and two experienced intracranial hemorrhage in the basal ganglia within 2 years of follow-up. Another patient was uncooperative and took medication arbitrarily. After excluding these five patients, we analyzed the demographic and imaging data from 127 subjects for the present study. Levodopa dose was defined as the dose taken at the time of development of LID in patients with LID or at the time of last visit in those without LID. The levodopa equivalent dose was calculated according to following formula: levodopa dose (X 1.33 if entacapone use) + (ropinorole X 20) + (pramipexole X 100) + (selegiline X 10) + amantadine.[22] Motor symptoms were assessed using the Unified PD Rating Scale (UPDRS) motor score (part III). We received approval from the Yonsei University Severance Hospital Ethical Standards Committee on Human Experimentation to conduct this study

with human subjects.

2. ^{18}F-FP-CIT PET

^{18}F-FP-CIT PET scans were performed with a GE PET-CT DSTe scanner (GE Discovery STE, GE Healthcare Technologies, Milwaukee, WI, USA), which obtains images with three-dimensional resolution of 2.3 mm full width at half-maximum. All subjects fasted for at least 6 hours before PET scanning. After fasting, 5mCi (185 MBq) of ^{18}F-FP-CIT was injected intravenously, and images were acquired in a three-dimensional mode at 120 KVp and 380 mAs during a 20-minutes session that occurred 90 minutes following injection.

3. Quantitative analysis of ^{18}F-FP-CIT PET data

Quantitative analyses were performed following a modified version of a previously described procedure.[23] Image processing was performed using SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) under Matlab 6.5.1 for Windows (Math Works, Natick, MA, USA) and MRIcro version 1.37 (Chris Rorden, Columbia, SC, USA). Quantitative analyses were based on volumes of interest (VOIs), which were defined based on a template in standard space. All reconstructed PET images were spatially normalized to Talairach space using a standard ^{18}F-FP-CIT PET template which was made using ^{18}F-FP-CIT PET and T-1 MR images of 13 normal controls to remove inter-subject anatomical variability. Eight VOIs of bilateral striatal subregions and one occipital VOI were drawn on a co-registered spatially normalized single T-1 MR and ^{18}F-FP-CIT PET template image. The striatum

was divided into the caudate, ventral striatum, anterior putamen, and posterior putamen. The VOI for the ventral striatum was defined according to previously defined criteria,[24] and the boundary between the anterior and posterior putamen was the anterior commissure coronal plane. The outer boundaries of striatal subregions were visually determined by the characteristic dense gray signal of the striatum, which readily distinguished these subregions from adjacent structures. Nine VOIs were tested against each subject's spatially normalized ^{18}F-FP-CIT PET image and adjusted when necessary. DAT activity was calculated by non-displaceable binding potential (BP_{ND}), which was defined as (mean standardized uptake value of the striatal subregions VOI – mean standardized uptake value of the occipital VOI)/mean standardized uptake value of the occipital VOI.[25]

4. Statistical analyses

We first compared the demographic and PET data of patients with and without LID. Chi-square tests were used for categorical variables, and independent *t* tests and Mann-Whitney U tests were used for continuous variables. Cox proportional hazard models were then conducted to identify the factors predictive of LID. Demographic factors with a significance level lower than 0.1 were selected for inclusion in Cox proportional hazard models; on this basis, age at onset of PD, sex, levodopa dose, and body weight as well as the DAT activity of each striatal subregion were included the analyses as independent variables. Next, DAT activities according to ^{18}F-FP-CIT uptake were divided into tertiles based on their distributions. We evaluated the association between

degree of DAT reduction and LID development using Cox proportional hazard models and log-rank tests. The subgroup with higher DAT activity was designated as the reference.

III. RESULTS

1. Demographic characteristics

The demographic characteristics of a total of 127 participants are presented in Table 1. The mean age at onset of PD was 62.9 years, and 53 (41.7%) patients were male. Subjects were diagnosed a median of 1.0 year (range, 0–5.4) after onset of motor symptoms, and the mean UPDRS motor score was 22.7. During a mean follow-up period of 3.4 years (range, 2.1–5.0), 35 patients with PD (27.6%) developed LID. Patients with LID were more likely than were those without LID to be female (74.3 vs. 52.2 %, $p = 0.028$) and to have higher UPDRS motor scores (29.6 vs. 20.5, $p = 0.001$). Patients with LID also tended to be younger at onset age of motor symptoms (60.3 vs. 63.9 years, $p = 0.083$), weigh less (58.7 vs. 62.5 kg, $p = 0.056$), and be treated with higher dose of levodopa (470.7 vs. 408.7 mg, $p = 0.095$) compared with those without LID. Additionally, patients with LID were treated with significantly higher levodopa equivalent dose (682.5 vs. 594.8 mg, $p = 0.028$), levodopa dose per kilogram (8.3 vs. 6.7 mg/kg, $p = 0.017$), and levodopa equivalent dose per kilogram (11.9 vs. 9.7 mg/kg, $p = 0.002$) compared with those without LID. There was no significant differences between groups in age at diagnosis, duration of motor symptoms prior to levodopa treatment, and use of other anti-parkinsonian drugs.

Table 1. Baseline characteristics of the subjects.

	Total (n = 127)	With LID (n = 35)	Without LID (n = 92)	P value
Age at diagnosis, yr	64.4 ± 10.5	62.0 ± 10.8	65.3 ± 10.3	0.112[a]
Number of female, n (%)	74 (58.3)	26 (74.3)	48 (52.2)	0.028[c]
Duration of motor symptom, yr	1.0 (0.5-2.0)	1.1 (0.4-3.0)	1.0 (0.5-2.0)	0.469[b]
Age at onset of PD, yr	62.9 ± 10.7	60.3 ± 11.2	63.9 ± 10.4	0.083[a]
UPDRS motor score*	22.8 ± 10.4	29.6 ± 10.1	20.5 ± 9.5	0.001[a]
Body weight, kg	61.5 ± 10.0	58.7 ± 9.5	62.5 ± 10.1	0.056[a]
Levodopa dose, mg	425.8 ± 187.2	470.7 ± 195.4	408.7 ± 182.2	0.095[a]
Levodopa equivalent dose, mg	619.0 ± 201.9	682.5 ± 227.6	594.8 ± 186.8	0.028[a]
Levodopa dose per kg of body weight, mg/kg	7.1 ± 3.4	8.3 ± 3.8	6.7 ± 3.1	0.017[a]
Levodopa equivalent dose per kg of body weight, mg/kg	10.3 ± 3.7	11.9 ± 4.5	9.7 ± 3.2	0.002[a]
Other drugs at development of dyskinesia or last visit				
Dopamine agonist, n(%)	92 (72.4)	24 (68.6)	68 (73.9)	0.547[a]
Selegiline, n(%)	31 (24.4)	8 (22.9)	23 (25.0)	0.802[a]
Entacapone, n(%)	50 (39.4)	17 (48.6)	33 (35.9)	0.191[a]
Amantadine, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Anticholinergics, n(%)	22 (17.3)	6 (17.1)	16 (17.4)	0.974[a]
Acetylcholinesterase inhibitor, n(%)	6 (4.7)	1 (2.9)	5 (5.4)	0.541[a]

Data are expressed as mean ± SD or n(%).

LID: levodopa-induced dyskinesia; UPDRS: Unified Parkinson's disease rating scale

*Data were obtained from 19 patients with LID and 55 without LID.

[a] Independent *t* test

[b] Mann-Whitney U test

[c] Chi-square test

2. DAT activity in the ^{18}F-FP-CIT PET

UPDRS motor scores were significantly correlated with DAT activity in the caudate (r = -0.53, p < 0.0001), ventral striatum (r = -0.43, p = 0.0002), putamen (r = -0.60, p < 0.0001), and striatum (r = -0.57, p < 0.0001). Comparison of ^{18}F-FP-CIT uptakes in the striatal subregions between groups are shown in Table 2. Patients with LID showed less DAT activity in the putamen (1.35 vs. 1.55, p = 0.040) than did those without LID, whereas DAT activity in the ventral striatum and caudate did not differ between groups. In the putamen, the difference in DAT activity between groups was greater in the posterior portion of the putamen (1.02 vs. 1.21, p = 0.029), and this difference was consistently observed in both the more (0.85 vs. 1.01, p=0.040) and the less affected (1.19 vs. 1.41, p = 0.037) sides.

3. Predictive value of DAT activity for the development of LID

Multivariate Cox regression hazard models were used to investigate the predictive value of DAT activity for the development of LID. The analyses revealed that the ^{18}F-FP-CIT uptake of the anterior putamen (hazard ratio [HR], 0.511; 95% confidential interval [CI], 0.289–0.905; p = 0.021), posterior putamen (HR, 0.272; 95% CI, 0.093–0.793; p = 0.017), and whole putamen (HR, 0.360; 95% CI, 0.158–0.818; p = 0.015) significantly predicted development of LID, whereas DAT activity in the caudate and ventral striatum was not significantly correlated with LID (Table 3). Additionally, younger age at onset of PD and higher dose of levodopa were significant predictors of LID.

Table 2. The ^{18}F-FP-CIT uptakes of striatal subregions. Data were calculated with non-displaceable binding pontential.

	More affected side			Less affected side			Mean putamen uptake		
	With LID	Without LID	p value	With LID	Without LID	p value	With LID	Without LID	p value
Caudate	1.63 ± 0.70	1.77 ± 0.67	0.301	1.92 ± 0.74	2.00 ± 0.77	0.578	1.77 ± 0.71	1.88 ± 0.67	0.419
Ventral striatum	1.82 ± 0.48	1.97 ± 0.55	0.152	2.13 ± 0.57	2.26 ± 0.63	0.385	1.97 ± 0.51	2.11 ± 0.58	0.220
Putamen	1.18 ± 0.35	1.35 ± 0.47	0.058	1.53 ± 0.48	1.76 ± 0.60	0.041	1.35 ± 0.40	1.55 ± 0.52	0.040
Anterior putamen	1.68 ± 0.52	1.88 ± 0.63	0.101	2.05 ± 0.66	2.31 ± 0.74	0.075	1.87 ± 0.58	2.10 ± 0.67	0.078
Posterior putamen	0.85 ± 0.26	1.01 ± 0.42	0.040	1.19 ± 0.41	1.41 ± 0.54	0.037	1.02 ± 0.32	1.21 ± 0.46	0.029

Data are expressed as mean ± SD.

LID: levodopa-induced dyskinesia

However, sex and body weight were not significantly associated with LID development. When levodopa equivalent dose instead of levodopa dose was incorporated in the multivariate Cox regression analysis, we found that the ^{18}F-FP-CIT uptake of the putamen remained a significant predictor of LID (p = 0.014), but that relationships between age at onset of PD and levodopa equivalent dose were less strongly associated with LID (age at onset of PD, p = 0.059; levodopa equivalent dose, p = 0.080).

Next, patients were grouped into tertiles based on the distribution of DAT activity on the ^{18}F-FP-CIT PET, and the highest tertile (the group showing a mild reduction in DAT uptake) was adopted as the reference group. The Cox proportional hazard models revealed that, compared with the mild-reduction group, patients having severe (HR, 3.449; 95% CI, 1.308–9.096; p = 0.012) and moderate (HR, 3.022; 95% CI, 1.162–7.862; p = 0.023) reductions in DAT activity in the whole putamen were at higher risk for the development of LID, whereas the risk for LID did not differ between patients with severe and those with moderate reduction in DAT activity (log-rank test, p = 0.046; Fig 1-A). Similarly, LID risk was higher in patients with severe and moderate reductions in DAT in the anterior putamen compared with those with mild DAT reduction (log-rank test, p = 0.049; Fig 1-B). In the posterior putamen, severe reduction in DAT activity was a significant predictor of the development of LID relative to moderate (HR, 2.297; 95% CI, 1.024–5.153; p = 0.044) or mild (HR, 3.552; 95% CI, 1.426–8.849; p = 0.006) DAT reduction (log-rank test, p = 0.008; Fig 1-C).

Table 3. Cox proportional hazard models for prediction of the time to development of levodopa-induced dyskinesia.

	Whole Putamen		Anterior Putamen		Posterior Putamen	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age at onset of PD	0.959 (0.928–0.992)	0.014	0.960 (0.929–0.992)	0.016	0.959 (0.928–0.992)	0.014
Female sex	2.211 (0.870–5.622)	0.096	2.285 (0.895–5.835)	0.084	2.023 (0.803–5.097)	0.135
Levodopa dose	1.002 (1.000–1.003)	0.043	1.002 (1.000–1.003)	0.036	1.002 (1.000–1.003)	0.042
^{18}F-FP-CIT uptake (BP_{ND})	0.360 (0.158–0.818)	0.015	0.511 (0.289–0.905)	0.021	0.272 (0.093–0.793)	0.017
Body weight	0.996 (0.957–1.037)	0.855	0.996 (0.956–1.036)	0.826	0.994 (0.956–1.035)	0.776

HR: hazard ratio; CI: confidential interval; PD: Parkinson's disease; BP_{ND}: non-displaceable binding potential.

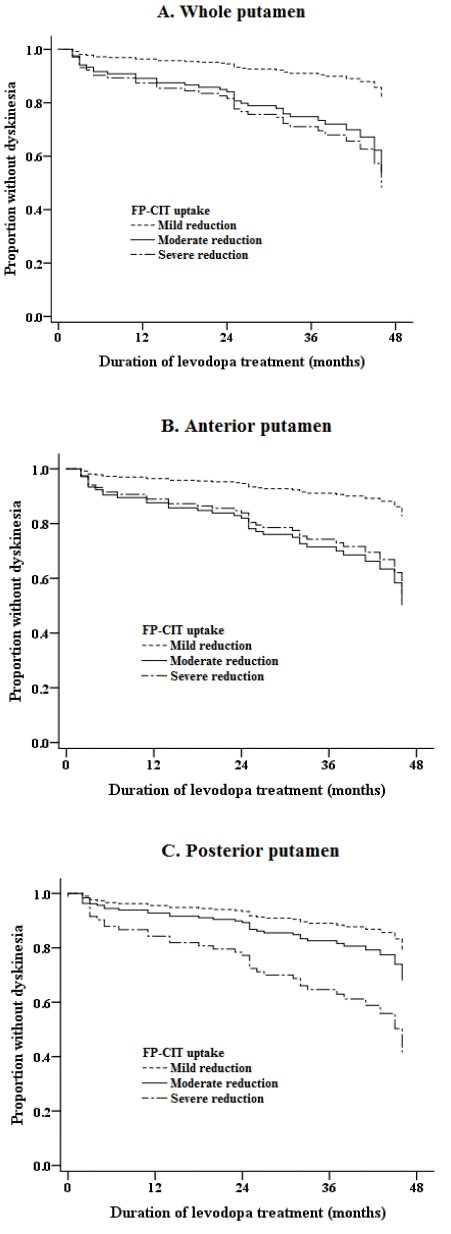

Figure 1. Survival curves of patients who did not show levodopa-induced dyskinesia according to the ^{18}F-FP-CIT uptake reduction in (A) the whole putamen, (B) the anterior putamen, and (C) the posterior putamen.

IV. DISCUSSION

Although presynaptic dopamine depletion has been theoretically considered essential for the development of LID, the association between degree of presynaptic dopamine denervation and risk of LID has been difficult to demonstrate. Several longitudinal studies explored the severity of parkinsonian motor symptoms as an indirect marker of presynaptic dopamine dysfunction; however, UPDRS motor scores are not precise reflections of the status of presynaptic dopamine denervation on PET or SPECT. Previous functional neuroimaging studies showed negative correlations between UPDRS motor scores and striatal DAT activity, but the strength of these correlations was not extremely high (r = -0.44 to -0.68).[26-28] Moreover, the UPDRS tremor[26,27] and rigidity[26] subscores were not correlated with presynaptic DAT activity, and postural and gait disturbance was strongly correlated with cholinergic rather than with nigrostriatal dopaminergic activity.[29] For this reason, several studies used functional imaging to evaluate the role of presynaptic dopamine depletion as a significant predictor of LID, but these studies did not employ a longitudinal design and thus were limited in their ability to draw definite conclusions.

In the present study, a quantifive analysis of ^{18}F-FP-CIT uptake demonstrated that DAT activity in the putamen, but not in the caudate, is a significant predictor of the development of LID. In terms of putaminal subregions, DAT activity in the posterior rather than the anterior putamen seems to be closely associated with LID development. From an anatomical perspective, the posterior putamen is a sensorimotor sector,[30] and experimental studies have

shown that the molecular events leading to LID in the context of presynaptic dopamine depletion are generally more pronounced in this region.[31,32] Indeed, a previous cross-sectional study also showed that ^{18}F-fluorodopa uptake in the putamen, but not the caudate, was related to the development of LID.[18] Additionally, several functional neuroimaging studies demonstrated that striatal dopaminergic denervation in patients with PD was most pronounced in the putamen, especially the postero-dorsal area,[33,34] and subregional differences in this tendency were more pronounced in the early stage of PD.[34] Therefore, development of LID seems to be associated with the subregional vulnerability to PD of the posterior putamen as well as with molecular events that induce this disease process.

As another considering point, the Cox proportional hazard models in the present study showed that the degree of DAT activity required to induce LID may differ by putaminal subregion; severe dopamine depletion, relative to mild or moderate depletion, was associated with LID in the posterior putamen, whereas moderate dopamine depletion, relative to mild dopamine depletion, was an additional predictor of LID in the anterior putamen. This result is unexpected, and it is difficult to explain the underlying pathomechanisms. According to animal studies of LID, the striatal subregions in which LID-associated mRNAs or proteins are strongly expressed may differ slightly, implying that the threshold for LID in the striatum may differ by region.[31,35] Moreover, Morissette et al. provided evidence for regional effects of the molecular signaling involved in the development of LID and suggested the possibility that the associative sector, as well as the sensorimotor area, of the putamen may contribute to the

development of LID.[31] Thus, it is possible that fact that the threshold for LID is lower in the anterior than in the posterior putamen may explain the difference in LID-associated DAT activity in the putamen. However, additional studies are required to examine this issue.

Postsynaptic changes have recently been recognized as important consideration in understanding LID. Super sensitivity of postsynaptic dopamine receptors and the influence of neurotransmitters other than dopamine seem to be involved the development of LID.[12] A cross-sectional PET study also showed that the characteristics of LID were related to both presynaptic and postsynaptic dopaminergic status.[19] More recently, Pons et al. reported LID in patients with thyrosine hydroxylase deficiency, which has normal presynaptic innervation.[36] It seems that presynaptic dopaminergic denervation is not necessary for the development of LID. However, the exogenous replacement of levodopa in response to thyrosine hydroxylase deficiency can lead to super sensitivity of postsynaptic receptors under conditions of dopamine depletion in the synaptic cleft. Therefore, presynaptic dopamine depletion, whether due to neuronal degeneration or functional impairment, remains a prerequisite for the development of LID.

The multivariate Cox proportional hazard models indicated that higher dose of levodopa and younger age at onset of PD were also significant predictors of LID. These risk factors have been reported consistently in many previous studies.[1,2,6,16] Additionally, female sex and body weight were significantly

associated with the development of LID in independent *t* tests and univariate Cox regression analyses, although this association was not significant in multivariate models. Generally, female subjects weigh less than males, and they therefore tend to receive relatively higher levodopa dose per unit of body weight. Thus, even though neither being female sex nor weighting less was an independent predictor of LID in the present studies, these factors may have an effect on the development of LID via their association with increased concentration of levodopa.[16] In the present study, the levodopa equivalent dose was not a significant predictor of LID. Dopamine agonists were frequently prescribed for our subjects, and it has been well established that LID develops less frequently in patients treated with dopamine agonists than with levodopa.[3,5]

The strengths and limitations of the present study need to be addressed. The present research is the first longitudinal study using a detailed quantification of DAT activity, and it included a relatively larger number of de novo patients with PD. Nevertheless, this study is limited in its ability to draw definitive conclusion due to its retrospective design. Second, we evaluated DAT activity at baseline but could not determine changes in this activity. As the degeneration of dopaminergic neurons did not follow a linear pattern and the rate of such degeneration also varied substantially,[34,37] further research regarding whether the rate of degeneration is predictive of development of LID is needed. Finally, this observational study did not include interventions related to dopaminergic medication. Controversy about whether dopamine agonists are neuroprotective, whether levodopa is toxic, and whether selegiline is neuroprotective

persists.[6,38-40] Although patients with and without LID did not differ in their use of anti-parkinsonian medications other than levodopa, it is possible that individual medication regimens may influence dopaminergic neuronal status or the development of LID.

V. CONCLUSION

Based on a detailed quantification of DAT activity, the present study demonstrated that PD patients with LID exhibited lower levels of initial DAT activity in the posterior putamen than did those without LID. Additionally, multivariate Cox regression hazard models showed that in addition to younger age at onset of PD and higher dose of levodopa, DAT activity in the putamen was a significant predictor of the development of LID in drug-naïve de novo PD patients. These data confirm that degree of presynaptic dopaminergic denervation plays a crucial role in the development of LID.

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< ABSTRACT (IN KOREAN)>

초기 파킨슨병 환자에서 시냅스전 도파민 고갈 정도와 레보도파유발 이상운동증 발생과의 연관성

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홍진용

파킨슨병 환자에서 시냅스전 도파민 고갈은 레도보파유발 이상운동증 발생에 필수적인 것으로 여겨지고 있으나, 이 관계는 연구에 의해 증명되지 않고 있다. 저자는 ^{18}F-FP-CIT 양전자방출단층촬영을 정량적으로 분석하여 시냅스전 도파민 고갈의 정도가 레보도파유발 이상운동증의 예측인자가 될 수 있는지 연구하였다.

진단 당시 ^{18}F-FP-CIT 양전자방출단층촬영을 하였고 진단 전에 약물을 복용하지 않았던 파킨슨병 환자를 모았다. 그 중 2년 이상 세브란스병원 신경과 외래 진료를 받아왔던 127명의 환자를 연구에 포함시켰고, 이 환자들은 매 3-6개월마다 신경과 외래를 방문하여 운동질환 전문의에게 진찰을 받았다. 이 환자들의 양전자방출단층촬영 자

료를 이용하여 정량적인 방법으로 각 소구역에서의 ^{18}F-FP-CIT 흡수율을 측정하였고, Cox 비례위험모형을 통해 이 흡수율의 레보도파 유발 이상운동증 발생에 대한 예측력을 계산하였다.

평균 3.4년 동안의 추적관찰기간동안 35명(27.6%)의 환자에서 레보도파유발 이상운동증이 발생하였다. 레보도파유발 이상운동증이 발생한 환자들은 그렇지 않은 환자들에 비해 조가비핵의 ^{18}F-FP-CIT 흡수율이 낮았다. Cox 비례위험모형을 통한 분석 결과, 전방과 후방, 그리고 전체 조가비핵에서의 흡수율은 레보도파유발 이상운동증 발생에 대한 유의한 예측인자였다. 꼬리핵과 배측 선조체 부위에서는 예측력이 없었다. 또한, 젊은 파킨슨병 발병 연령과 높은 레보도파 용량도 레보도파유발 이상운동증의 예측인자였다.

이 결과들은 시냅스전 도파민 고갈이 레보도파유발 이상운동증의 발생에 중요한 역할을 한다는 증거가 될 수 있다.

핵심되는 말 : 레보도파, 이상운동증, 파킨슨병, 시냅스전, FP-CIT, 양전자방출단층촬영