



저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

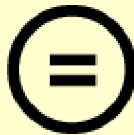
다음과 같은 조건을 따라야 합니다:



저작자표시. 귀하는 원저작자를 표시하여야 합니다.



비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.



변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 [이용허락규약\(Legal Code\)](#)을 이해하기 쉽게 요약한 것입니다.

[Disclaimer](#)

Does the pattern of
striatal dopamine depletion
contribute to non-motor symptoms
in Parkinson's disease?



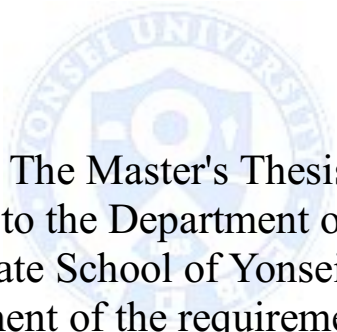
Su Jin Chung

Department of Medicine

The Graduate School, Yonsei University

Does the pattern of
striatal dopamine depletion
contribute to non-motor symptoms
in Parkinson's disease?

Directed by Professor Young H. Sohn



The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Su Jin Chung

June 2015

This certifies that the Master's Thesis
of Su Jin Chung is approved.

Thesis Supervisor : Young H. Sohn

Thesis Committee Member#1 : Phil Hyu Lee

Thesis Committee Member#2 : Sung-Rae Cho

The Graduate School
Yonsei University

June 2015

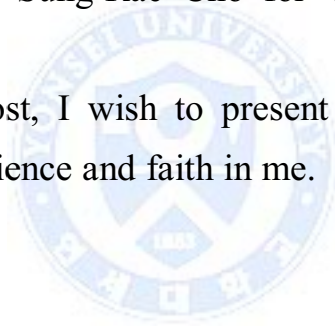
ACKNOWLEDGEMENTS

I am honored to sincerely thank all those who gave me the opportunity to complete this thesis.

First of all, I deeply appreciate my supervisor, professor Young H. Sohn for his guidance and encouragement. His comments helped a lot during the start up and finishing of this study.

I also would like to thank my instructor professor Phil Hyu Lee and professor Sung-Rae Cho for valuable advices and support.

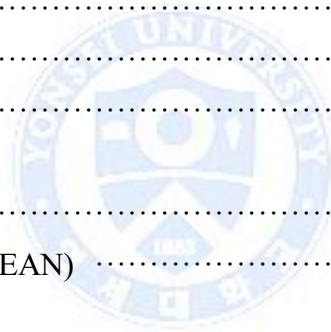
Last but the most, I wish to present my gratitude to my family for their patience and faith in me.



Su Jin Chung

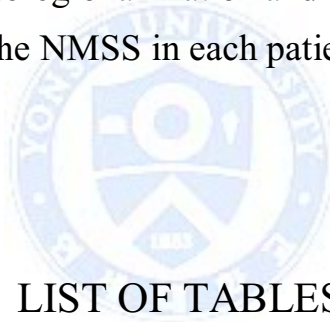
<TABLE OF CONTENTS>

ABSTRACT	1
I. INTRODUCTION	3
II. MATERIALS AND METHODS	5
1. Subjects	5
2. Assessment of non-motor symptoms	6
3. PET-CT image acquisition	7
4. Quantitative analysis of ^{18}F -FP-CIT PET data	7
5. Statistical analysis	10
III. RESULTS	10
IV. DISCUSSION	17
V. CONCLUSION	21
REFERENCES	22
ABSTRACT(IN KOREAN)	27



LIST OF FIGURES

Figure 1. Images of ^{18}F -FP-CIT uptakes at the level of striatum.	9
Figure 2. A scatterplot showing the relationship between DAT activity in the posterior putamen and UPDRS-motor score in each patient.	13
Figure 3. A scatterplot showing anterior putamen/posterior putamen inter-subregional ratio and the mood/cognition domain score of the NMSS in each patient.	16



LIST OF TABLES

Table 1. Clinical characteristics of the two patient groups	12
Table 2. ^{18}F -FP-CIT uptakes of striatal subregions and inter-subregional ratios between the two patient groups	14
Table 3. Correlation between ^{18}F -FP-CIT uptakes and the each domain score of the NMSS	15

ABSTRACT

Does the pattern of striatal dopamine depletion
contribute to non-motor symptoms in Parkinson's disease?

Su Jin Chung

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Young H. Sohn)

Background : Non-motor symptoms (NMS) has been recognized as a key determinant factor for quality of life in Parkinson's disease (PD), but the mechanism underlying NMS in PD has not yet been elucidated well. To investigate whether the pattern of striatal dopamine depletion contributes to NMS in PD, we hypothesized that PD patients with greater NMS might have a different pattern of striatal dopamine depletion, particularly the areas other than the posterior putamen, compared to those with less NMS.

Methods : We conducted a survey of the degree of NMS (using non-motor symptoms scale, NMSS) in 151 PD patients who had been initially diagnosed at our hospital by dopamine transporter (DAT) scanning, using a [¹⁸F] N-(3-Fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) PET scan (from March 2009 to June 2013).

Results : Patients with a high NMSS score (above the median) had an older age of PD onset (64.9 ± 9.1 vs 61.5 ± 10.1 years, $p = 0.034$), a higher initial part III

of the Unified Parkinson Disease rating scale (UPDRS-motor, assessed in drug-naïve state) (26.9 ± 11.7 vs 20.9 ± 10.3 , $p = 0.003$), a higher levodopa-equivalent dose (636.3 ± 293.0 vs 524.4 ± 196.2 , $p = 0.007$), and a greater Beck Depression Inventory (BDI) score (14.7 ± 8.1 vs 11.5 ± 7.5 , $p = 0.013$), compared to those with a low NMSS score. A general linear model showed that patients with a high NMSS score had significantly higher UPDRS-motor score than those with a low score after controlling for onset age, gender, symptom duration, BDI score, and DAT activity in the posterior putamen ($p = 0.034$). However, DAT activities in 6 striatal subregions and inter-subregional ratios (ISRs) were comparable between the two groups. There were no correlations between subregional DAT activities and NMSS scores (either total or each domain scores), except for the mood/cognition domain score, which was negatively correlated to the anterior putamen/posterior putamen ISR ($r = -0.175$, $p = 0.032$).

Conclusion : This study demonstrates that the pattern of striatal dopamine depletion does not contribute to the degree of NMS in early PD, although some clinical features are different between the patients with greater NMS and those with less NMS. This study also suggests that patients with less NMS may have a benign course of motor symptom progression, compared to those with more NMS. NMS in PD may be more likely associated with extra-striatal lesions accompanied in PD than striatal dopaminergic deficits.

Key words : non-motor symptoms; parkinson's disease; striatal dopamine depletion

Does the pattern of striatal dopamine depletion
contribute to non-motor symptoms in Parkinson's disease?

Su Jin Chung

*Department of Medicine
The Graduate School, Yonsei University*

(Directed by Professor Young H. Sohn)

I. INTRODUCTION

Parkinson's disease (PD) is a chronic degenerative disorder of the central nervous system, resulting in motor disability such as bradykinesia, rigidity, resting tremor, and postural instability. Besides motor symptoms, PD is also accompanied by variety of non-motor symptoms (NMS) involving sleep, mood, cognition, attention, and autonomic functions. NMS can occur across all stage of PD, and has been recognized as a key determinant factor for quality of life in PD patients. Some NMS such as olfactory deficit, constipation, rapid eye movement sleep behavior disorder (RBD), and depression may precede the motor symptoms by many years.¹ In contrast to the motor symptoms, NMS may be easily misdiagnosed, and may have inappropriate medical interventions.² Although the importance of NMS in PD has been widely recognized in recent years, the mechanism underlying NMS has not yet been elucidated well.

The motor symptoms of PD result mainly from the loss of dopaminergic

neurons in the substantia nigra, but PD pathology also involves widespread brainstem and cortical lesions with alterations of several neurotransmitters other than dopamine, such as serotonin, norepinephrine, and acetylcholine.³ Similar to motor symptom fluctuation, the presence of NMS fluctuation in advanced PD patients has been well recognized. Some NMSs are exacerbated during the off-period, suggesting a potential dopaminergic contribution. The importance of the dopaminergic contribution to NMS in PD was highlighted by a recent positron emission tomography (PET) study, in which dopaminergic depletion in the hypothalamus is associated with the development of sleep, endocrine, and autonomic dysfunctions.⁴ A number of clinical trials have demonstrated a beneficial effect of specific dopaminergic drugs on some NMSs, such as RBD, pain, restless leg syndrome, and depression.⁵ However, a majority of NMSs may seldom respond to PD medications, and some of them can even be exacerbated by dopaminergic treatments. Thus, the pathophysiological mechanism underlying NMS in PD is still unclear, and appears to be more heterogeneous than pure dopaminergic deficits.⁶

Dopamine transporter (DAT) activity, since it represents the integrity of presynaptic dopaminergic neurons in the striatum, has been widely used as an imaging biomarker for the diagnosis of PD. Accordingly, various techniques using different radioligands have been developed for this purpose, and used in clinical practice. Among them, [¹⁸F] N-(3-Fluoropropyl)-2 β -carbon ethoxy-3 β -(4-iodophenyl) nortropane (FP-CIT) PET has been available in Korea as well as in our hospital since 2008.⁷ Compared to DAT single photon emission computed tomography (SPECT), ¹⁸F-FP-CIT PET has better spatial

resolution and more sophisticated attenuation correction, and can be used to evaluate subregional changes in the striatal DAT.⁸ Compared to healthy people, DAT activity is significantly reduced in all areas of the striatum in PD patients, but the degree of reduction is different among the striatal subregions. In PD patients, DAT reduction in the posterior putamen is much greater than that in other striatal subregions.^{9,10} In addition, inter-subregional ratios (ISRs) are also different among various parkinsonism, suggesting the diverse patterns of striatal dopaminergic depletion specific to different parkinsonism syndromes.¹⁰

Therefore, we performed this study to investigate whether the pattern of striatal dopamine depletion contributes to NMS accompanied in PD. We hypothesized that PD patients with greater NMS might have a different pattern of striatal dopamine depletion, particularly the striatal subregions other than the posterior putamen, compared to those with less NMS. Secondly, in this study, we also investigated whether early PD patients with greater NMS have different clinical features compared to those with less NMS.

II. MATERIALS AND METHODS

1. Subjects

We conducted a survey of the degree of NMS (using Korean version of the non-motor symptoms scale, NMSS) in PD patients who had been initially diagnosed at our hospital by DAT scanning, using a ¹⁸F-FP-CIT PET scan (from March 2009 to June 2013). PD in these patients was diagnosed according to the clinical criteria of the UK PD Brain Bank,⁸ the presence of appropriate DAT defects on ¹⁸F-FP-CIT PET scans,¹⁰ and the presence of PD drug response

during follow-up (≥ 18 months). The interpretation of ^{18}F -FP-CIT-PET scans was performed by nuclear medicine physicians who were blind to the clinical status of each patient. For this study, we excluded the patients with having focal lesions or lacunar infarctions in the basal ganglia, those with atypical parkinsonism or secondary parkinsonism, those having severe medical illness which could affect NMS, and those were taking dopaminergic medication in other hospital already. The part III of the Unified Parkinson Disease rating scale (UPDRS-motor) and modified Hoehn and Yahr stage (HYS) were used to assess PD motor severity at the time of the diagnosis. Mini-mental State Examination (MMSE), Beck Depression Inventory (BDI), and Cross Cultural Smell Identification Test (CCSIT)¹¹ were performed as a routine diagnostic work-up. Parkinsonian medications prescribed at the time of NMSS assessment were checked, and levodopa-equivalent dose (LED) was calculated on the basis of previously described methodology.¹² We received approval from the Ethics committee of our hospital for experiments using human participants.

2. Assessment of non-motor symptoms

The original NMSS was developed for NMS assessment in PD patients by the International Parkinson's Disease Non-Motor Group,¹³ and has been widely used in clinical studies of PD. The Korean version of the NMSS has been developed and validated.¹⁴ The NMSS is composed of thirty items that are grouped to the nine domains: cardiovascular including falls (2 items), sleep/fatigue (4 items), mood/cognition (6 items), perceptual problems/hallucinations (3 items), attention/memory (3 items), gastrointestinal

tract (3 items), urinary (3 items), sexual function (2 items), and miscellaneous (4 items; pain, taste or smell, weight change, and excessive sweating). Score for each item is based on a multiple of severity (from 0 to 3) and frequency scores (from 1 to 4). The total NMSS score ranged from 0 to 360, in which higher score represents more severe NMS. The NMSS was rated by a neurologist, and obtained through interviews of the patients and their caregivers.

3. PET-CT image acquisition

^{18}F -FP-CIT PET scans were used with a GE Discovery STe (DSTE) PET-CT scanner (GE Healthcare Technologies, Milwaukee, WI). DAT images were obtained with 3D resolution, and performed a post hoc 3D Gaussian smoothing with 2.3 mm full width at half maximum. After fasting for at least 6 hours before PET scanning, 5 mCi (185 MBq) of ^{18}F -FP-CIT was injected intravenously. Images were taken in a 3D mode at 120 KVp and 380 mAs during a 20- minute session that came about 90 minutes after injection.

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

Quantitative analyses of ^{18}F -FP-CIT PET data were fulfilled through a previously described procedure.¹⁰ Image processing was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) under MATLAB 2013a for Windows (MathWorks, Natick, MA). Quantitative analyses were based on volumes of interests (VOIs), which were defined based on a template in standard space. All reconstructed PET images were spatially normalized to Montreal Neurology Institute (MNI) template

space using a standard ^{18}F -FP-CIT PET template, which was made using ^{18}F -FP-CIT PET and T1 MRI of 13 normal controls to remove inter-subject anatomical variability. Twelve VOIs of bilateral striatal subregions and one occipital VOI were drawn on a co-registered spatially normalized single T1 MRI and ^{18}F -FP-CIT PET template image on MRICro version 1.37 (Chris Rorden, Columbia, SC), based on previous study (Figure 1).¹⁰ These VOIs were adjusted by a minor translation in our in-house VOI editing software called ANTIQUE.¹⁵ Using DAT activity concentration in each VOI, we estimated the surrogate of nondisplaceable binding potential (BP_{ND}), defined as follows: (mean standardized uptake value [SUV] of the striatal subregions VOI - mean SUV of the occipital VOI)/mean SUV of the occipital VOI.¹⁶ We used mean BP_{ND} for each bilateral striatal subregions. The ISR was defined as the ratio of DAT activity of one striatal subregion to that of another striatal subregion. Posterior putamen was used to the common denominator, and 5 ISRs were calculated.

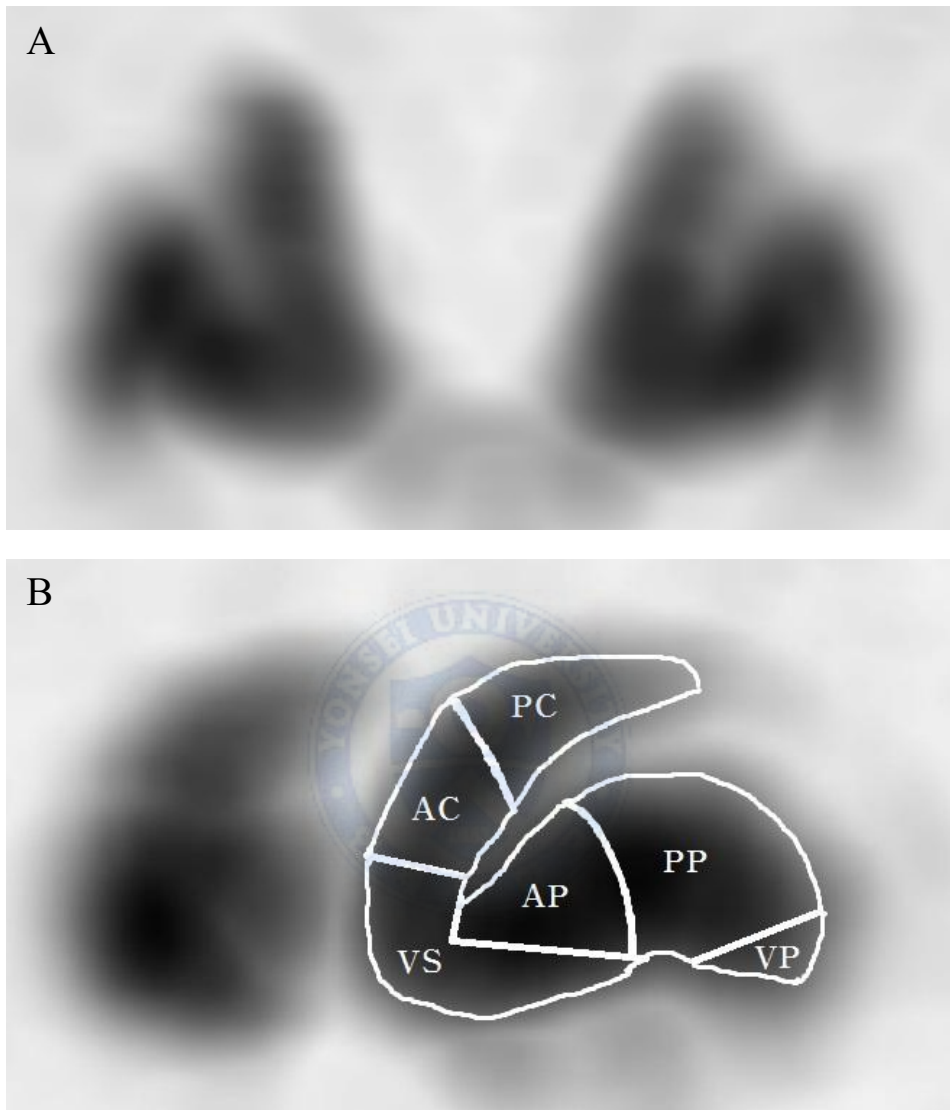


Figure 1. Images of ^{18}F -FP-CIT uptakes at the level of striatum. A healthy control (A), and diagram of 6 striatal subregions (B).

VS: ventral striatum, AC: anterior caudate, PC: posterior caudate, AP: anterior putamen, PP: posterior putamen, VP: ventral putamen.

5. Statistical analysis

Data were expressed as means \pm SDs. We divided the patients into two groups according to their total NMSS scores (above the median and the median or less). An independent *t* test was used to compare numeric variables, and χ^2 test was used to compare categorical variables between the patients with greater NMS and those with less NMS. A general linear model was used to compare the difference of UPDRS-motor score between the two groups after controlling for onset age, gender, duration of motor symptoms, BDI score, and DAT activity in the posterior putamen. A partial correlation analysis was conducted to evaluate the relationship between striatal subregional DAT activity and the NMSS scores (total and each domain scores), after controlling for the follow-up duration (intervals from DAT scan to the NMSS). SPSS Statistics 20 (IBM SPSS, Armonk, NY, USA) was used to perform all statistical analyses. *P*-values <0.05 were regarded as significant.

III. RESULTS

One hundred and fifty-one patients (mean age, 67.9 ± 9.6 years; range, 41 – 88 years; 67 men) were included in this study. Total NMSS score in each patient ranged from 0 to 169 (mean, 45.5 ± 34.0 ; median, 37). Seventy-six (50.3%) patients belonged to the low NMSS group (total NMSS ≤ 37), while seventy-five (49.7%) patients were in the high NMSS group (total NMSS > 37). Clinical characteristics of the two patient groups are shown in Table 1. High NMSS patients were older PD onset age (64.9 ± 9.1 vs 61.5 ± 10.1 years, $p = 0.034$), had a higher initial UPDRS-motor score (26.9 ± 11.7 vs 20.9 ± 10.3 , $p =$

0.003), more severe initial HYS ($p = 0.017$), a higher LED at follow-up (636 ± 293 vs 524 ± 196 , $p = 0.007$), and a higher BDI score (14.7 ± 8.1 vs 11.5 ± 7.5 , $p = 0.013$), compared to low NMSS patients. A general linear model showed that high NMSS patients had significantly higher UPDRS-motor score than low NMSS patients after controlling for onset age, gender, duration of motor symptoms, BDI score, and DAT activity in the posterior putamen ($p = 0.034$) (Figure 2). However, DAT activities in 6 striatal subregions and ISRs were comparable between the two groups (Table 2).



Table 1. Clinical characteristics of the two patient groups

	Low NMSS score (n=76)	High NMSS score (n=75)	<i>p</i> -value
Onset age (years)	61.5 ± 10.1	64.9 ± 9.1	0.034
Gender (% man)	44.7	44.0	0.927
Education (years)	10.0 ± 4.7	8.9 ± 5.9	0.248
Duration of motor symptoms (years)	1.2 ± 0.9	1.5 ± 1.3	0.058
Follow-up duration (years)	3.3 ± 1.2	3.5 ± 1.3	0.297
Initial UPDRS-motor score	20.9 ± 10.3	26.9 ± 11.7	0.003
Initial Hoehn and Yahr stage (%)			0.017
1.0/1.5	34.8	20.0	
2.0/2.5	62.1	64.6	
3.0/4.0	3.0	15.4	
Levodopa-equivalent dose (mg)	524.4 ± 196.2	636.3 ± 293	0.007
MMSE score	25.9 ± 2.9	25.6 ± 3.6	0.631
BDI score	11.5 ± 7.5	14.7 ± 8.1	0.013
CCSIT score	6.9 ± 2.5	6.9 ± 2.6	0.847

Data are means ± SDs.

UPDRS: Unified Parkinson's Disease rating scale, MMSE: Mini-Mental State Examination, BDI: Beck Depression Inventory, CCSIT: Cross Cultural Smell Identification Test.

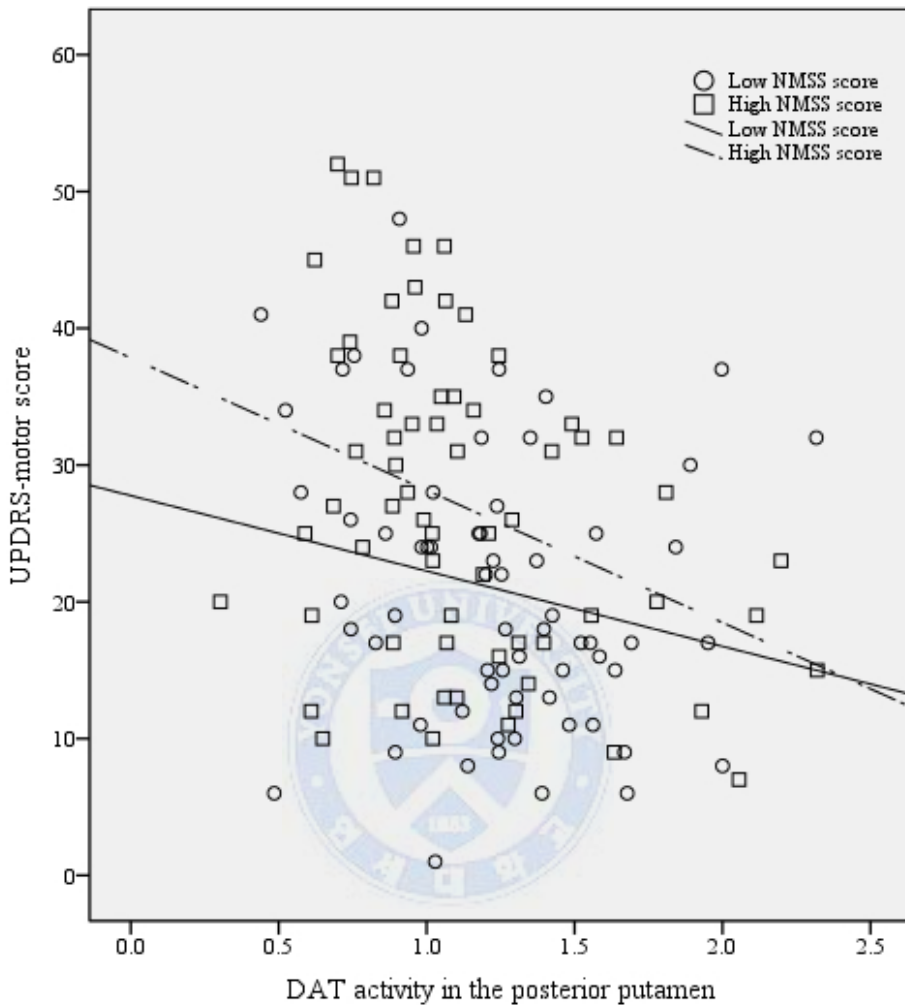


Figure 2. A scatterplot showing the relationship between DAT activity in the posterior putamen and UPDRS-motor score in each patient. Low NMSS score patients (circle) represent significantly lower UPDRS-motor score at same DAT activity in the posterior putamen than high NMSS score patients (rectangle).

Table 2. ^{18}F -FP-CIT uptakes of striatal subregions and inter-subregional ratios between the two patient groups

	Low NMSS score (n=76)	High NMSS score (n=75)	<i>p</i> -value
Striatal subregions			
VS	2.38 ± 0.57	2.32 ± 0.66	0.578
AC	2.09 ± 0.67	2.11 ± 0.83	0.873
PC	1.30 ± 0.47	1.32 ± 0.56	0.811
AP	2.13 ± 0.60	2.06 ± 0.68	0.510
PP	1.21 ± 0.39	1.19 ± 0.44	0.690
VP	1.40 ± 0.37	1.34 ± 0.40	0.367
Inter-subregional ratios			
AP/PP	1.82 ± 0.41	1.81 ± 0.42	0.919
AC/PP	1.78 ± 0.53	1.85 ± 0.58	0.443
VP/PP	1.19 ± 0.19	1.18 ± 0.23	0.877
VS/PP	2.09 ± 0.69	2.12 ± 0.70	0.797
PC/PP	1.09 ± 0.31	1.16 ± 0.40	0.282

Data are means ± SDs.

VS: ventral striatum, AC: anterior caudate, PC: posterior caudate, AP: anterior putamen, PP: posterior putamen, VP: ventral putamen.

The correlations between subregional DAT activities and the each domain score of the NMSS after controlling for follow-up duration are shown in Table 3. The mood/cognition domain score significantly and negatively correlated to the anterior putamen/posterior putamen ISR ($r = -0.175$, $p = 0.032$) (Figure 3). In contrast, the cardiovascular and sleep/fatigue domain scores positively correlated with the anterior caudate/posterior putamen ISR. The other NMSS domain scores and total NMSS score did not correlate to subregional DAT activities.

Table 3. Correlation between ^{18}F -FP-CIT uptakes and the each domain score of the NMSS

	Cardio-vascular	Sleep/Fatigue	Mood/Cognition	Perceptual/Hallucinations	Attention/Memory	Gastro-intestinal	Urinary	Sexual function	Miscellaneous	Total
Inter-subregional ratios										
AP/PP	0.091	0.067	-0.175*	-0.011	-0.067	0.042	-0.068	0.060	-0.134	-0.079
AC/PP	0.184*	0.176*	-0.117	0.087	0.029	0.030	-0.095	0.034	-0.034	-0.004
VP/PP	0.108	0.016	-0.063	-0.015	-0.061	0.079	-0.124	-0.014	-0.036	-0.053
VS/PP	0.159	0.047	-0.116	0.054	-0.037	0.133	-0.043	0.013	-0.079	-0.020
PC/PP	0.156	0.157	-0.081	0.086	0.041	0.069	-0.089	0.083	0.034	0.034

Significant difference across groups, $*p < 0.05$.

VS: ventral striatum, AC: anterior caudate, PC: posterior caudate, AP: anterior putamen, PP: posterior putamen, VP: ventral putamen.

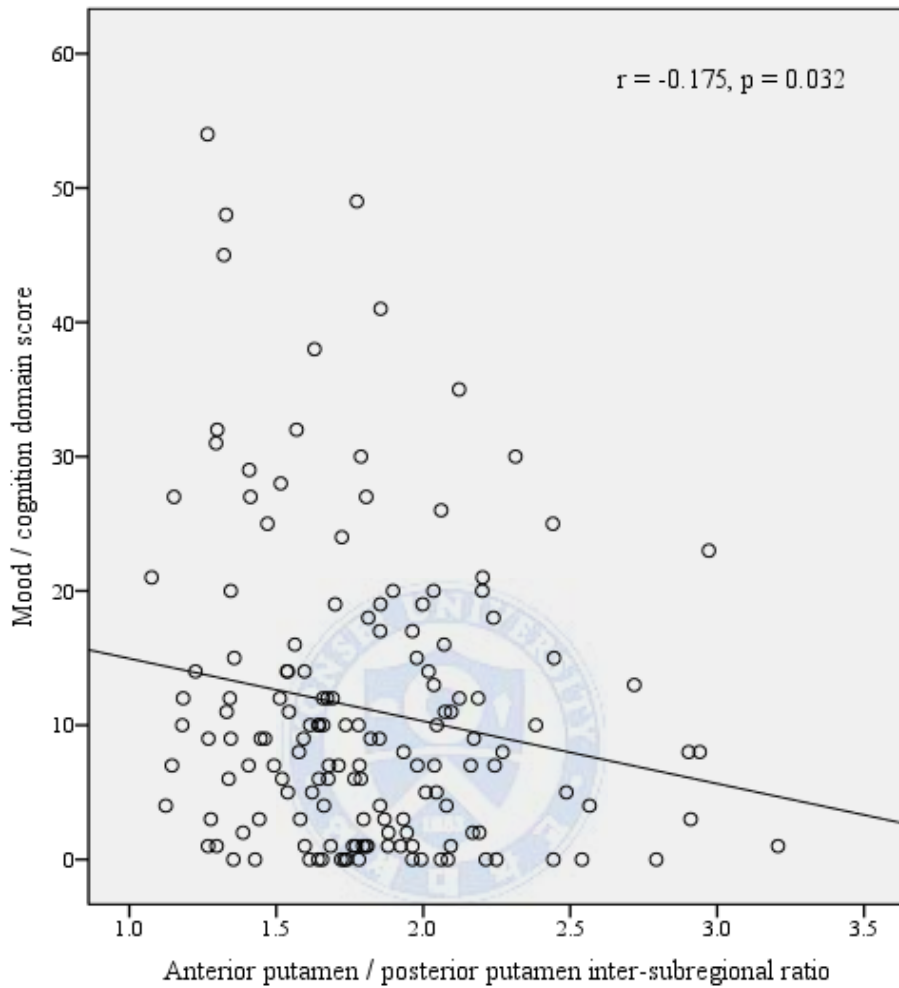


Figure 3. A scatterplot showing anterior putamen/posterior putamen inter-subregional ratio and the mood/cognition domain score of the NMSS in each patient. There is significant negative correlation after adjustment for follow-up duration.

IV. DISCUSSION

This study demonstrated that high NMSS patients showed different clinical characteristics, such as an older onset age, more severe motor symptoms, and more severe depression, when compared to low NMSS patients. DAT activities in the striatal subregions and ISRs in high NMSS patients were similar to those in low NMSS patients. After controlling DAT activity in the posterior putamen as well as onset age, gender, motor symptom duration and BDI score in each patient, UPDRS-motor scores were still higher in high NMSS patients than low NMSS patients. This result suggests that low NMSS patients shows either a more benign course or a greater reserve compensating for the pathological processes when compared to high NMSS patients. Less LED in low NMSS patients when compared to that in high NMSS patients after similar follow-up duration support this assumption. Although the total NMSS score did not correlated to ISRs, the mood/cognition domain score correlated inversely and significantly with the anterior putamen/posterior putamen ISR, and the cardiovascular and sleep/fatigue domain scores correlated positively and significantly to the anterior caudate/posterior putamen ISR. The inverse relationship between mood/cognition and the anterior putamen/posterior putamen ISR suggests that patients with greater DAT defects in the anterior putamen relative to those in posterior putamen shows greater deficits in mood/cognition function. However, the meaning of the positive relationship between cardiovascular, sleep/fatigue and the anterior caudate/posterior putamen ISR is uncertain and might be incidental, because it is hard to explain how greater DAT defects in the anterior caudate is associated with less

cardiovascular and sleep/fatigue dysfunction.

The mean NMSS score in our patients was relatively lower than that in the original study,¹³ presumably because we enrolled early stage PD patients. The association between NMS and PD progression has been well documented in a number of studies, in which a number of NMS increases along with PD duration, HYS, and UPDRS scores.^{13,17} In this study, high NMSS patients also showed a higher UPDRS-motor score than low NMSS patients, which is compatible to the previous studies. Because depression is a main component of the mood/cognition domain of the NMSS, and could be an important factor influencing other NMS such as sleep/fatigue, attention/memory, and so on, it is fully expected that high NMSS patients had a higher BDI score, i.e., a greater depression, than low NMSS patients. In this study, high NMSS patients were older at PD symptom onset than low NMSS patients. Because many of NMSs can be associated with aging in healthy people, this result is also predictable like as previous study.¹⁸

PD symptoms do not develop until 50 - 60% of the dopaminergic neurons in the substantia nigra are lost,¹⁹ suggesting the presence of a mechanism for compensation in the motor system. The ability of the brain to show no functional impairment until the damage reaches a critical threshold, which is called compensatory ability, may reflect an individual's neuronal reserve.²⁰ Similarly, in the present study, the low NMSS patients showed less motor deficits when compared to the high NMSS patients, despite a similar degree of striatal dopamine reduction in the posterior putamen. Therefore, PD patients with less NMS represent either a more benign course or a greater reserve

compensating for the pathological process when compared to those with greater NMS.

The mood/cognition domain of the NMSS contains apathy, anxiety, fear, depression, and dysthymia. Depression, anxiety, and apathy belong to the most common hypodopaminergic behavioral syndrome in PD patients.²¹ Previous research that used [¹¹C]RTI-32 PET (an in vivo marker of both dopamine and noradrenaline transporter binding) detected decreased binding in the locus coeruleus and in several regions of the limbic system including the anterior cingulate cortex, thalamus, amygdala and ventral striatum in PD patients with depression and anxiety. In addition, apathy was inversely correlated with [¹¹C]RTI-32 binding in the ventral striatum, not in the caudate or the putamen.²² A previous study performed in PD patients has shown an association between depression and altered putamen metabolism.²³ Among the studies using DAT SPECT, one showed that anxiety and depression were associated with reduced DAT activity in the left anterior putamen,²⁴ while the other demonstrated that anxiety severity was related with reduced DAT activity in the right caudate.²⁵ Thus, previous studies suggest a potential connection between affective symptoms in PD and striatal DAT reduction, although this assumption is still controversial. The present result showing an association between the degree of NMS and DAT reduction in the anterior putamen may provide an additional evidence to support the above assumption.

Recent studies have demonstrated that excessive daytime sleepiness and RBD in early PD patients are correlated with decreased striatal DAT binding.^{26 27} Another study has also shown that fatigue in PD is related to reduced

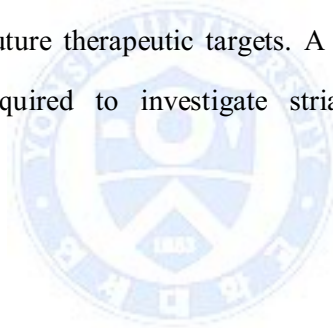
dopaminergic function in the caudate and the insula.²⁸ In this study, the anterior caudate/posterior putamen ISR was positively correlated with the sleep/fatigue domain score, which is quite opposite to the results shown in the above studies. In addition, the anterior caudate/posterior putamen ISR was also positively correlated with the cardiovascular domain score. Dopamine has a complex role in the sleep-wake cycle, and, in PD, sleep-related problems might be dopamine sensitive.²⁹ Also, the sleep/fatigue domain contains diverse symptoms of sleep, such as hypersomnia and insomnia, while the cardiovascular domain is only composed of two questions. These factors could have effect on distinct result from previous studies. Thus, it is hard to explain how greater DAT reduction is associated with less NMS, these results appear to be an incidental rather than a clinically relevant finding.

In this study, other NMSS domain scores were not correlated to striatal subregional ISRs. Previous studies have shown that reduced DAT uptakes in the caudate, ventral striatum, and anterior cingulate cortex are associated with cognitive impairment in PD,^{30,31} while another study using ¹⁸F-Dopa PET have demonstrated no significant correlation between cognitive abilities of non-demented PD and striatal dopaminergic depletion.³²

Selection of de novo PD patients in this study minimized the influence of any PD medication on the assessments of striatal dopamine depletion and motor deficits. A programmed measure of striatal dopamine activities could minimize the inter- and intra-rater variability. However, a longitudinal follow-up study is warranted to assess whether PD patients with less NMS show more benign course of PD progression.

V. CONCLUSION

This study demonstrates that the pattern of striatal dopamine depletion does not contribute to the degree of NMS in early PD, although some clinical features are different between the patients with greater NMS and those with less NMS. Our research also suggests that patients with less NMS may have a more benign course of motor symptom progression or a greater reserve compensating for the pathological process, compared to those with more NMS. NMS in PD may be more likely associated with extra-striatal lesions accompanied in PD than striatal dopaminergic deficits. Further functional imaging study that handle pathogenesis underlying NMS in PD should be necessary, and it will be able to contribute to develop future therapeutic targets. A prospective and long term follow-up study is required to investigate striatal dopaminergic system associated with NMS.



REFERENCES

1. Chaudhuri KR, Naidu Y. Early Parkinson's disease and non-motor issues. *J Neurol* 2008;255 Suppl 5:33-8.
2. O'Sullivan SS, Williams DR, Gallagher DA, Massey LA, Silveira-Moriyama L, Lees AJ. Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. *Mov Disord* 2008;23:101-6.
3. Modugno N, Lena F, Di Biasio F, Cerrone G, Ruggieri S, Fornai F. A clinical overview of non-motor symptoms in Parkinson's Disease. *Arch Ital Biol* 2013;151:148-68.
4. Politis M, Piccini P, Pavese N, Koh SB, Brooks DJ. Evidence of dopamine dysfunction in the hypothalamus of patients with Parkinson's disease: an in vivo ^{11}C -raclopride PET study. *Exp Neurol* 2008;214:112-6.
5. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 2009;8:464-74.
6. Papapetropoulos S, Mash DC. Psychotic symptoms in Parkinson's disease. From description to etiology. *J Neurol* 2005;252:753-64.
7. Park E. A new era of clinical dopamine transporter imaging using ^{123}I -FP-CIT. *J Nucl Med Technol* 2012;40:222-8.
8. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:745-52.

9. Wang J, Zuo CT, Jiang YP, Guan YH, Chen ZP, Xiang JD, et al. ^{18}F -FP-CIT PET imaging and SPM analysis of dopamine transporters in Parkinson's disease in various Hoehn & Yahr stages. *J Neurol* 2007;254:185-90.
10. Oh M, Kim JS, Kim JY, Shin KH, Park SH, Kim HO, et al. Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy. *J Nucl Med* 2012;53:399-406.
11. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). *Laryngoscope* 1996;106:353-6.
12. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25:2649-53.
13. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. *Mov Disord* 2007;22:1901-11.
14. Koh SB, Kim JW, Ma HI, Ahn TB, Cho JW, Lee PH, et al. Validation of the korean-version of the nonmotor symptoms scale for Parkinson's disease. *J Clin Neurol* 2012;8:276-83.
15. Oh JS, Oh M, Chung SJ, Kim JS. Cerebellum-specific ^{18}F -FDG PET analysis for the detection of subregional glucose metabolism changes in spinocerebellar ataxia. *Neuroreport* 2014;25:1198-202.

16. Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* 2007;27:1533-9.
17. Khoo TK, Yarnall AJ, Duncan GW, Coleman S, O'Brien JT, Brooks DJ, et al. The spectrum of nonmotor symptoms in early Parkinson disease. *Neurology* 2013;80:276-81.
18. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, Mitra T, Frades-Payo B, Tluk S, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. *Mov Disord* 2010;25:704-9.
19. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* 1991;114 (Pt 5):2283-301.
20. Palmer SJ, Ng B, Abugharbieh R, Eigenraam L, McKeown MJ. Motor reserve and novel area recruitment: amplitude and spatial characteristics of compensation in Parkinson's disease. *Eur J Neurosci* 2009;29:2187-96.
21. Thobois S, Ardouin C, Schmitt E, Lhomme E, Klinger H, Xie J, et al. Behavioral disorders in Parkinson's disease: from pathophysiology to the mastery of dopaminergic treatment. *Rev Neurol (Paris)* 2010;166:816-21.
22. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain* 2005;128:1314-22.
23. Mentis MJ, McIntosh AR, Perrine K, Dhawan V, Berlin B, Feigin A, et

- al. Relationships among the metabolic patterns that correlate with mnemonic, visuospatial, and mood symptoms in Parkinson's disease. *Am J Psychiatry* 2002;159:746-54.
24. Weintraub D, Newberg AB, Cary MS, Siderowf AD, Moberg PJ, Kleiner-Fisman G, et al. Striatal dopamine transporter imaging correlates with anxiety and depression symptoms in Parkinson's disease. *J Nucl Med* 2005;46:227-32.
25. Erro R, Pappata S, Amboni M, Vicidomini C, Longo K, Santangelo G, et al. Anxiety is associated with striatal dopamine transporter availability in newly diagnosed untreated Parkinson's disease patients. *Parkinsonism Relat Disord* 2012;18:1034-8.
26. Happe S, Baier PC, Helmschmied K, Meller J, Tatsch K, Paulus W. Association of daytime sleepiness with nigrostriatal dopaminergic degeneration in early Parkinson's disease. *J Neurol* 2007;254:1037-43.
27. Eisensehr I, Linke R, Tatsch K, Kharraz B, Gildehaus JF, Wetter CT, et al. Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. *Sleep* 2003;26:507-12.
28. Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain* 2010;133:3434-43.
29. Ng KY, Chase TN, Colburn RW, Kopin IJ. Dopamine:

stimulation-induced release from central neurons. *Science* 1971;172:487-9.

30. Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M, et al. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [^{18}F]fluorodopa positron emission tomographic study. *Arch Neurol* 2000;57:470-5.
31. Ito K, Nagano-Saito A, Kato T, Arahata Y, Nakamura A, Kawasumi Y, et al. Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: a 6- ^{18}F fluoro-L-dopa PET study. *Brain* 2002;125:1358-65.
32. Broussolle E, Dentresangle C, Landais P, Garcia-Larrea L, Pollak P, Croisile B, et al. The relation of putamen and caudate nucleus ^{18}F -Dopa uptake to motor and cognitive performances in Parkinson's disease. *J Neurol Sci* 1999;166:141-51.

ABSTRACT(IN KOREAN)

파킨슨병 환자에서 선조체의 도파민 감소가 비운동 증상에
기여하는가?

<지도교수 손영호>

연세대학교 대학원 의학과

정수진

목적 : 파킨슨병의 비운동 증상은 삶의 질에 영향을 미치는 주요한
요인으로 알려져 있으나, 이에 대한 정확한 병태생리는 정립된 바가
없다. 선조체 도파민의 감소 양상이 파킨슨병의 비운동 증상에
영향을 미치는지 알아보기 위하여, 본 연구는 비운동 증상이 심한
파킨슨병 환자일수록 뒤쪽 조가비핵보다 오히려 다른 부위의
선조체에 도파민 신경세포의 감소율이 심할 것이라고 가정하였다.

방법 : 본원에서 2009년 3월부터 2013년 6월까지 파킨슨병을 처음
진단받았고, 진단 당시에 [¹⁸F] N-(3-Fluoropropyl)-2β-carbon
ethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) 양전자 방출
단층촬영을 시행한 151명의 환자를 대상으로 비운동 증상 평가 척도
(NMSS)를 작성하였다.

결과 : 비운동 증상 평가 척도의 점수가 높은 (중앙값 이상) 환자들이

점수가 낮은 환자들에 비하여 발병연령이 높았고 (64.9 ± 9.1 vs 61.5 ± 10.1 years, $p = 0.034$), 초기의 통합파킨슨병척도운동점수 (UPDRS-motor)가 높았으며 (26.9 ± 11.7 vs 20.9 ± 10.3 , $p = 0.003$), 레보도파 일용량이 높았고 (636.3 ± 293.0 vs 524.4 ± 196.2 , $p = 0.007$), 백 우울척도 (BDI) 점수가 높았다 (14.7 ± 8.1 vs 11.5 ± 7.5 , $p = 0.013$). 발병연령, 성별, 이환기간, 백 우울척도 점수 및 뒤쪽 조가비핵의 도파민 활성도를 보정한 후의 일반선형모형에서는 비운동 증상 평가 척도의 점수가 높은 환자들의 통합파킨슨병척도운동점수가 의미있게 높았다. 그러나 선조체 6구역과 소구역간의 비 (ISRs)는 두 군간에 차이가 없었다. 비운동 증상 평가 척도의 기분/인지 영역의 점수는 앞쪽 조가비핵/뒤쪽 조가비핵의 도파민 활성화도 소구역간의 비와 음의 상관관계를 보였으나 ($r = -0.175$, $p = 0.032$), 총 점수 및 다른 영역의 점수와 선조체 소구역의 도파민 활성화도 간에는 의미있는 상관관계가 없었다.

결론 : 본 연구는 선조체 도파민의 감소 양상이 초기 파킨슨병의 비운동 증상에 영향을 미치지 않는지만, 비운동 증상이 심한 환자와 경한 환자 사이에 임상 양상의 차이가 난다는 점을 나타낸다. 또한 비운동 증상이 경한 환자들은 운동 증상의 진행이 더디다는 것을 시사한다. 파킨슨병의 비운동 증상은 선조체의 도파민 감소보다는 파킨슨병과 연관된 선조체 외의 병변으로 인하여 초래될 것이다.

핵심되는 말 : 비운동 증상; 파킨슨병; 선조체 도파민 감소