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Original Research

Striatal Subregion Analysis Associated with REM Sleep Behavior Disorder in Parkinson's Disease

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Abstract

Background and Purpose: REM sleep behavior disorder (RBD) in Parkinson's disease (PD) is associated with characteristic clinical subtypes and prognosis. In addition, nigrostriatal pathway, the most vulnerable anatomical area in PD, formed neuronal network interplaying with cortical and subcortical structures, and which may cause PD clinical phenotype. We evaluated the regional selectivity of presynaptic striatal dopaminergic denervation associated with RBD in PD. **Methods**: We compared two groups (n = 16) of PD patients with and without RBD in terms of specific binding ratios (SBR) in subregions of the striatum, which were measured using positron emission tomography with 18F-FP-CIT. SBRs of the anterior and posterior caudate, ventral striatum, and posterior and ventral putamen regions were measured in more or less affected side, and right or left side, or bilateral sum of the striatum. **Results**: Age, disease duration, and severity of parkinsonism were not significantly different between groups. Although group differences in all areas were not significant with multiple comparison corrections, SBR of the ventral striatum and anterior caudate in sum of both sides was significantly less in the RBD than in the non-RBD group without correction ($p < 0.05$). In the right anterior caudate and left ventral striatum, SBR was also lower in the RBD than in the non-RBD group without correction ($p < 0.05$). Attention function was impaired in the RBD group compared with the non-RBD group ($p < 0.05$). However, these statistical significances were not definite after correction of multiple comparisons ($p > 0.05$). **Conclusions**: There is a possibility that RBD in early PD may be associated with presynaptic dopaminergic denervation in the ventral striatum and anterior caudate, which may explain decreased attention in our RBD group. RBD in PD may imply a distinct pathological progression. However, further study using large numbers of participants or longitudinal observation is necessary for the statistical conclusion because of small sample size.

Keywords: REM sleep behavior disorder; Parkinson's disease; striatal binding ratio; attention

1. Introduction

REM sleep behavior disorder (RBD) is commonly observed in several neurodegenerative diseases, especially in synucleinopathy, which includes Parkinson's Disease (PD). A total of 30%–60% of patients with PD present with RBD during their disease course; patients with RBD seem to be a distinct clinical entity compared with patients with PD without RBD [1,2]. Previous cross-sectional studies have reported poorer motor features, cognitive dysfunction, and hallucination in PD with RBD compared with PD without RBD, and a longitudinal study has reported poorer clinical outcomes with RBD [3–5]. However, it is unknown why PD with RBD showed distinct clinical phenotype.

Neuronal damage causing parkinsonism is mainly on the degeneration of nigrostriatal pathway in PD. In addition, striatum has wide connection with various anatomical structures including cortex and other subcortical areas, hence, subregional difference in striatal degeneration can contribute to clinical phenotype of PD. Considering PD with RBD have a distinct clinical entity compared to PD without RBD, there is a possibility of subregional difference in the striatal degeneration associated with RBD. Nonetheless, the denervation pattern in the striatal subregions has never been evaluated according to the existence of RBD in PD. In this study, we aimed to investigate whether the nigrostriatal degeneration pattern differs between patients with RBD and those without RBD (non-RBD) with early-stage PD who are naïve to drug therapy.

2. Methods

2.1 Study Design and Subjects

Thirty-two consecutive patients with PD who visited our neurology clinic for the first time and met following inclusion and exclusion criteria were enrolled in the study. PD was diagnosed using the Movement Disorder Society clinical diagnostic criteria by movement specialists [6]. We included consecutive patients with PD who were older than 30 years, drug-naïve, and had a disease duration of less than 3 years at enrolment. Clinical dementia was excluded. Brain magnetic resonance imaging (MRI) was performed to exclude patients with structural lesions in subcortical structure including the nigrostriatal area, cortical area, and brain stem. For the diagnosis of PD, positron emission tomography using 18F-FP-CIT was performed in all participants. Participants with a clinical diagnosis of dementia, stroke, other neurological disorders were excluded. And polysomnography was done in all participants to reveal the existence of RBD. Use of offending drugs causing RBD and severe obstructive sleep apnea to disturb the diagnosis of RBD were excluded. This study was approved by our institution's ethical committee (IRB 2019-06-008).

2.2 Acquisition of Dopamine Transporter Imaging and Volume of Interest

Dopamine transporter imaging via 18F-FP-CIT (Philips GEMINI TF-64, 7146, Philips, USA) obtained images with three-dimensional resolution of 2.3 mm full width at half maximum. All subjects did not take medication which can disturb ligand bining. PET emission acquisition was performed at 3 hours for 15 minutes in the three-dimensional mode after 5 mCi injection of 18F-FP-CIT injection after brain CT scan, which was performed in the axial helix at 120 Kvp and 200 mAs. And PET image was reconstructed from CT data by all-pass filter with a 512 $\times$ 512 matrix. Image processing was done by statistical parametric mapping (SPM) 8 (SPM8, Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, United Kingdom) within MATLAB R2014a (The MathWorks, Inc, Natick, Ma, USA) and ITK-SNAP (http://www.itksnap.org). 18F-FP-CIT PET/CT images were rigidly registered to the corresponding T1-weighted MRI. T1-weighted MRIs were spatially normalized to the Montreal Neurology Institute (MNI) template space. Then, the deformation field derived from MRI normalization was applied to 18F-FP-CIT images for the spatial normalization of PET images. Volumes of interests (VOI) were drawn on the MNI template and used for quantitative analyses for 18F-FP-CIT images. The VOI of 18F-FP-CIT uptake was measured in six areas of the striatum, relative to the uptake in the occipital region. This ratio is referred to as the specific binding ratio (SBR). We measured the SBR of anterior and posterior caudate (AC, PC), ventral striatum (VS), anterior and posterior putamen (AP, PP), and ventral putamen (VP).

2.3 Assessment of RBD

The diagnosis of RBD was based on history of dream enactment behavior and via polysomnographic confirmation of excessive electromyography activity in REM sleep proposed by the International Classification of Sleep Disorders (ICSD)-2 [7]. We recruited patients without RBD who had no clinical history confirmed by polysomnography.

2.4 Other Variables

To assess the motor and nonmotor status of parkinsonism, the Movement Disorder Society Unified Parkinson Disease Rating Scale and Hoehn and Yahr's scale were measured at baseline. Initial clinical features were characterized as tremor dominant, Akineto-rigidity and gait disturbance by a chief complaint. Attention, language, visuospatial memory, and frontal functions were assessed using the Seoul Neuropsychological Screening Battery, a neuropsychological battery consisting of standardized, validated tests, including the Montreal Cognitive Assessment. The Seoul Neuropsychological Screening Battery in this study included the following: (1) forward and backward digit span, (2) the Korean version of the Boston Naming test, (3) the Rey–Osterrieth Complex Figure Test, (4) the Seoul Verbal Learning Test, (5) contrasting program/go-no-go test, (6) the Controlled Oral Word Association Test, and (7) the Stroop test (color reading). For each test, specific norms for comparisons based on age, sex, and education, which were based on assessments of 447 normal Korean participants, were used to transform the data into z-scores [8].

2.5 Statistical Analysis

SBR in six striatal areas was compared between the RBD and non-RBD group in the left and right sides of the striatum, the more and less affected sides, or bilateral sum. The more affected side was defined as that with the lower SBR between the right and left striatum. The Mann–Whitney U test or the Chi-squared test was used to compare demographical features, other clinical variables, and SBR between the two groups. The Benjamini-Hochberg multiple comparison correction was calculated because multiple tests for each striatal areas were done. A p value of <0.05. was considered statistically significant. Statistical analyses were performed using SPSS ver 26.0 (IBM, Armonk, NY, USA).

3. Results

Table 1 shows the different demographic and clinical features of the RBD and non-RBD groups. Age, gender, and clinical features related to parkinsonism (disease duration, akineto-rigid phenotype, Hoehn and Yahr's scale, and Unified Parkinson Disease Rating Scale) were not significantly different between the two groups ($p > 0.5$ for all). Global cognition, assessed using the Montreal Cognitive Assessment test, did not differ significantly between the groups ($p = 0.254$).

Table 1. Demographic and clinical features of participants.

	Non-RBD (n = 16)	RBD (n = 16)	*p*
Age	57.00 ± 8.34	62.44 ± 8.24	0.094
Gender (M/F)	7/9	10/6	0.479
Disease duration	1.63 ± 1.11	0.83 ± 1.04	0.539
Initial clinical manifestation (tremor/AR/GD)	10/3/3	9/5/2	0.686
Hoehn & Yahr (1/2/3)	5/10/1	1/12/3	0.146
UPDRS part I	1.44 ± 1.15	1.63 ± 2.00	0.809
UPDRS part II	5.93 ± 4.18	7.00 ± 4.07	0.533
UPDRS part III	22.13 ± 11.31	25.13 ± 8.47	0.361
MOCA	25.06 ± 2.93	25.00 ± 7.10	0.254
MMSE	28.31 ± 1.74	27.38 ± 1.96	0.163

Abbreviations: AR, Akineto-rigidity; GD, gait disturbance.

Among the six striatal areas, the PP area showed the lowest SBR values in both RBD and non-RBD groups and in all participants ($p < 0.001$, analysis of variance). Comparing the other areas, the VS area had lower SBR in the RBD group than in the non-RBD group in the less and more affected side of the striatum ($p = 0.032$ and $p = 0.026$, respectively). The bilateral sum SBR values of the AC and VS areas had lower SBR in the RBD group than in the non-RBD group ($p = 0.046$ and $p = 0.020$, respectively). However, this statistical significance was not definite after multiple comparison correction ($p > 0.05$ in all). In the other areas (PC, AP, PP, and VP) there was no significant difference in SBR between the two groups even without multiple comparison corrections (Table 2, Fig. 1).

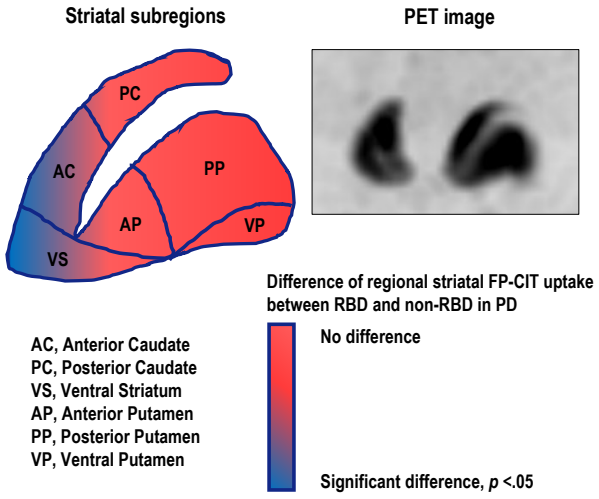

Fig. 1. Tophography of 6 striatal areas and the areas showing different value according to the existence of RBD in PD. AC and VS area showed lower striatal binding in the RBD group compared to non-RBD group.

Comparing the left and right sides of the striatum, the left VS had significantly lower SBR in the RBD group than in the non-RBD group ($p = 0.017$); the right VS showed a moderate difference ($p = 0.051$). In addition, the right AC had lower SBR in the RBD group than in the non-RBD group ($p = 0.047$) (**Supplementary Table 1**). However, this statistical significance was not definite after multiple comparison correction ($p > 0.05$ in all).

In cognitive assessment, the forward digit span in attention domain and the Controlled Oral Word Association Test (animal) assessment of frontal/executive function were decreased in the RBD group compared with the non-RBD group ($p = 0.35$ and $p = 0.32$, respectively). Across the five cognitive domains, the RBD group had a significantly decreased attention function compared with the non-RBD group ($p = 0.022$). There were no statistically significant differences between the groups in the other cognitive domains (language, visuospatial memory, and frontal function) (Table 3). Dysfunction in attention domain was well correlated with SBR in VS ($r = 0.358$, $p < 0.05$, **Supplementary Table 2**).

4. Discussion

We evaluated subregional differences in presynaptic dopaminergic neurodegeneration of the striatum with regard to RBD in drug-naïve patients with early PD. Overall, striatal SBR was significantly decreased in the PP area, as expected, irrespective of RBD; however, in the AC and VS areas, which are relatively well preserved in early PD, the RBD group had a significantly lower uptake than the non-RBD group in this study.

Striatal degeneration in PD shows a distinctive spatial and temporal pattern during the course of the disease. In PD, a degeneration pattern with an anteroposterior gradient has been reported in previous literature [9]. This pattern is quite different from the Parkinson Plus syndrome [9]. From the early stage of PD, the PP area is the most affected; this corresponds well with the pattern of neurodegeneration in the substantia nigra, i.e., early degeneration of the ventrolateral substantia nigra, which was demonstrated in autopsy studies [10,11]. This pattern was common in all our study patients irrespective of RBD. The severity of degeneration in the PP area did not differ between the RBD and non-RBD

Table 2. The comparison of SBR in detailed striatal areas of more/less affected area in the patients with RBD and without it.

Side	Region	Non-RBD (n = 16)	RBD (n = 16)	*p*
More affected side	Whole striatum	12.93 ± 4.38	11.12 ± 3.26	0.195
	AC	3.03 ± 1.11	2.41 ± 0.81	0.160
	PC	1.89 ± 1.01	1.43 ± 0.77	0.239
	VS	2.90 ± 0.68	2.38 ± 0.66	0.032
	AP	2.43 ± 0.94	2.26 ± 0.63	0.838
	PP	0.90 ± 0.41	0.97 ± 0.39	0.305
	VP	1.79 ± 0.61	1.68 ± 0.38	0.724
Less affected side	Whole striatum	15.92 ± 4.94	12.81 ± 3.66	0.053
	AC	3.47 ± 1.17	2.63 ± 0.85	0.073
	PC	2.09 ± 0.99	1.58 ± 0.85	0.160
	VS	3.26 ± 0.72	2.61 ± 0.70	0.026
	AP	3.17 ± 1.09	2.60 ±0.64	0.224
	PP	1.47 ± 0.59	1.30 ± 0.56	0.423
	VP	2.45 ± 0.75	2.09 ± 0.46	0.196
Sum of both side	Whole striatum	28.85 ± 9.26	23.93 ± 6.84	0.098
	AC	6.50 ± 2.27	5.04 ± 1.64	0.046
	PC	3.98 ± 1.99	3.01 ± 1.61	0.136
	VS	6.16 ± 1.37	4.98 ± 1.34	0.020
	AP	5.60 ± 2.00	4.86 ± 1.24	0.222
	PP	2.37 ± 0.97	2.26 ± 0.90	0.751
	VP	4.23 ± 1.31	3.77 ± 0.82	0.244

Values indicate mean ± standard deviations.

Abbreviations: AC, Anterior Caudate; PC, Posterior Caudate; VS, Ventral Striatum; AP, Anterior Putamen; PP, Posterior Putamen; VP, Ventral Putamen; Both side means sum of more and less affected sides.

All *p* value was uncorrected for multiple comparisons. And *p* values using Benjamini-Hochberg multiple comparison correction were not significant (all *p* value > 0.05).

groups. However, among the relatively preserved areas of the striatum, uptake in the AC and VS differed significantly between the groups according to the presence or absence of RBD.

The PP area has a primary connection with the motor cortical area, which may explain why motor dysfunction is prominent in early PD [12]. The VS area may have strong connectivity with the ventromedial prefrontal cortex and orbitofrontal cortex, which may imply that it has limbic and attentional functions [12,13]. Similarly, the AC area is connected to the prefrontal cortex and the major parts of the orbitofrontal cortex or dorsal anterior cingulate cortex [13]. From these connection, the VS and AC areas are associated with emotional and cognitive function. Although we did not evaluate reward or emotional aspects sufficiently, our cognitive assessments indicated that attentional deficit was prominent in the RBD group; this dysfunction may be associated with the different neurodegeneration levels observed in the AC or VS area or both.

There have been few positron emission tomography imaging studies comparing the patterns of nigrostriatal dopaminergic degeneration in PD between individuals with and without RBD. Arnaldi *et al.* [14,15] used I^{123}-FP-CIT–single-photon emission computerized tomography (SPECT) in patients with PD with and without RBD. They found that patients with PD and RBD had worse cognitive function and more severe nigrostriatal dopaminergic impairment in the caudate area of the less affected hemisphere than those without RBD [14,15]. Our previous study using I^{123}-FP-CIT-SPECT of 416 patients with *de novo* PD (from the Parkinson's Progression Markers Initiative study cohort) found that dopamine transporter uptake did not differ between RBD and non-RBD groups at baseline; however, during 4 years of follow-up, striatal SBR was found to decrease faster in the RBD group that in the non-RBD group. Furthermore, the caudate area showed greater denervation, compared with the putamen area [16]. However, previous studies have been limited by the low resolution of SPECT imaging, making it difficult to distinguish the striatal subregions. SPECT imaging can analyze striatal dopaminergic density only in two regions, the caudate and putamen. Our results show low density in the AC and VS areas in the RBD group, which is markedly different from previous findings. Our study clarifies that the ill-defined area named "caudate" in SPECT imaging can be divided into the AC and VS subregions.

Table 3. The comparison of neuropsychological test in patients with RBD and without RBD.

Neuropsychological domain	Neuropsychological test (max score)	Non-RBD (n = 16)	RBD (n = 16)	*p*
Attention	Forward digit span (9)	0.29 ± 0.69	–0.35 ± 0.71	0.035
	Backward digit span (8)	–0.40 ± 0.49	–0.48 ± 0.43	0.445
Language	K-BNT (60)	0.33 ± 0.77	0.21 ± 0.79	0.669
Visuospatial	RCFT (copying) (36)	0.05 ± 0.88	0.33 ± 1.29	0.642
Memory	SVLT (immediate recall) (36)	–0.63 ± 1.19	–0.73 ± 0.93	0.799
	SVLT (delayed recall) (12)	–0.27 ± 1.30	–0.60 ± 1.01	0.341
	SVLT (recognition) (24)	–0.18 ± 0.87	–0.12 ± 1.05	0.809
	True positive + false negative			
	RCFT(immediate recall) (36)	–0.28 ± 1.045	–0.34 ± 1.18	0.926
	RCFT(delayed recall) (36)	–0.16 ± 1.03	–0.41 ± 1.24	0.564
	RCFT (recognition) (24)	–0.03 ± 1.05	0.18 ± 0.95	0.381
	True positive + false negative			
Frontal/Executive function	Contrasting program (20)	20.00 ± 0.000	20.00 ± 0.000	1.000
	Go-no-go test (20)	19.88 ± 0.342	18.75 ± 4.74	0.985
	COWAT (animal)	0.23 ± 0.77	–0.36 ± 0.76	0.032
	COWAT (supermarket items)	0.06 ± 1.25	–0.09 ± 1.17	0.724
	COWAT (phonemic fluency)	–0.17 ± 1.02	–0.27 ± 0.99	0.985
	Stroop test: color reading (112)	0.18 ± 0.71	0.14 ± 0.97	0.897
SNSB_II_Domain_Attention		–0.02 ± 0.53	–0.56 ± 0.60	0.022
SNSB_II_Domain_Language		0.50 ± 0.62	0.30 ± 0.77	0.619
SNSB_II_Domain_Visuospatial		0.20 ± 0.81	0.01 ± 0.82	0.531
SNSB_II_Domain_Memory		–0.24 ± 1.12	–0.47 ± 1,13	0.449
SNSB_II_Domain_frontal		0.44 ± 0.93	–0.11 ± 1.06	0.215

All *p* value was uncorrected for multiple comparisons. And *p* values using Benjamini-Hochberg multiple comparison correction were not significant (all *p* value > 0.05).

Although our study has a limitation in that multiple test corrections by Bonferroni did not find any significant statistical differences, this study is an exploratory study design and has a small sample size. However, this study did not demonstrate the statistical difference in multiple comparisons, it should be evaluated in larger scale or longitudinal design. Therefore, based on the current study, further study is required for the interpretation of these findings. Nevertheless, we used polysomnography to confirm RBD, unlike previous studies that used clinical diagnoses to establish RBD. Although we included only a small number of patients, this study has methodological merits because RBD confirmed by polysomnography increased sensitivity for determining RBD-related characteristics.

5. Conclusions

The regional selectivity of nigrostriatal degeneration may be observed in PD with RBD compared with PD without RBD implies that there are different clinical phenotypic presentations. It remains unknown why this differential degeneration pattern occurs in PD. Thus, further investigation using large scale is required for statistical confirmation.

Author Contributions

IK, investigation and data curation, original draft preparation. YKL, investigation and data curation, original draft preparation. HM, and YJK, investigation and data curation. SL, investigation and data curation, review and editing of manuscript. MY, investigation and data curation, review and editing of manuscript. HSH, Investigation, review and final preparation of review and editing of manuscript. YEK, investigation, data curation, original draft preparation, review and final preparation of review and editing of manuscript.

Ethics Approval and Consent to Participate

This study was approved by Hallym University Sacred Heart Hospital Institution's ethical committee (IRB 2019-06-008). Informed consent was waived by IRB because medical records were used only for this study.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2201018.

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