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Association of autonomic symptoms with presynaptic striatal dopamine depletion in drug-naive Parkinson's disease: An analysis of the PPMI data

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ABSTRACT

While the involvement of the central and peripheral autonomic networks is thought to play an integral role in the development of autonomic symptoms in Parkinson's disease (PD), there is little evidence for an association between autonomic symptoms and striatal dopaminergic depletion. We compared dopamine transporter activity in striatal subregions with various autonomic symptoms covered by the SCOPA-AUT domains including gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual symptoms in 418 untreated patients with PD. We found evidence for a dopaminergic association with only urinary symptoms. Moreover, dopaminergic denervation in the putamen but not in the caudate may underlie these symptoms.

1. Introduction

Patients with Parkinson's disease (PD) experience a broad spectrum of autonomic symptoms (Muller et al., 2011). A previous study showed that gastrointestinal autonomic symptoms occurred in 56% of patients with PD who had a mean disease duration of 10 years, while urinary and/or sexual symptoms occurred in 64% of patients, thermoregulatory in 35%, cardiovascular in 18%, and pupillomotor in 19% (Merola et al., 2018). The burden and range of these symptoms are one of the key determinants of quality of life (Merola et al., 2018; Muller et al., 2011).

The involvement of the central and peripheral autonomic networks reportedly plays an integral role in the development of autonomic symptoms in PD (Coon et al., 2018). With respect to the central autonomic network, a recent study using functional magnetic resonance imaging showed disrupted thalamo-striato-hypothalamic functional connectivity in patients with PD with autonomic symptoms (Dayan et al., 2018). There has been also evidence suggesting the contribution of striatal dopaminergic deficiency to autonomic symptoms. Previous functional imaging studies have shown that patients with PD with urinary symptoms had lower dopamine transporter (DAT) activity in the striatum compared with those without urinary symptoms (Sakakibara et al., 2001; Winge et al., 2005). However, these observations were obtained from a low number of patients and were limited because the patients used dopaminergic medications which can influence autonomic symptoms. On the other hand, it is unclear whether dopaminergic defects in the striatum contribute to other autonomic symptoms. Therefore, this study aimed to assess the relationship between striatal dopaminergic depletion and various autonomic symptoms in patients with untreated PD.

2. Methods

2.1. Study design and participants

The Parkinson's Progression Markers Initiative (PPMI) is an ongoing international multicenter, observational cohort study aimed at identifying biomarkers that predict the heterogeneous progression of PD. The methodology and details of the study assessments are available on the PPMI website (http://ppmi-info.org/study-design).

The data were downloaded from the PPMI database on March 21, 2018. The current analysis included 418 newly diagnosed, drug-naive patients with PD who had the Scale for Outcome in Parkinson's Disease-Autonomic (SCOPA-AUT) and ^{123}I-FP-CIT single photon emission computed tomography (SPECT) data collected at enrollment (either at screening or the baseline visit). Each participating PPMI site received approval from the appropriate ethical standards committee on human experimentation before the start of the study and obtained written informed consent for research from all participating individuals in the study.

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2.2. Variables

Autonomic symptoms were evaluated using the SCOPA-AUT, which has high internal construct validity (Forjaz et al., 2010). The following six subscales were independently rated: gastrointestinal (7 items), urinary (6 items), cardiovascular (3 items), thermoregulatory (4 items), pupillomotor (1 item), and sexual (2 items for men and 2 items for women). In this study, each of these autonomic domains was regarded as impaired if at least one of the associated items was rated ≥2 (0 = never; 1 = sometimes; 2 = regularly; and 3 = often) (Merola et al., 2018).

^{23}I-FP-CIT SPECT was conducted during the screening visits. The standard operating procedures for DAT SPECT imaging have been previously described in detail (Kim et al., 2018). For this analysis, we used the mean DAT uptake of the left and right sides of the caudate and putamen.

Oher clinical variables included in this study were age at enrollment, sex, disease duration, age at onset, and the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score and total score to evaluate disease severity, and the Montreal Cognitive Assessment score to evaluate overall cognitive status.

2.3. Statistical analysis

By design, all patients with PD included in the PPMI database have abnormal DAT imaging. Thus, the participants in this study were divided into tertiles (mild, moderate, and severe reduction) based on the DAT uptake level of each striatal subregion. We used the Pearson chi-squared test for categorical parameters and one-way analysis of variance (ANOVA) for continuous parameters to compare the demographic and clinical data. Post-hoc analyses were conducted with the Bonferroni method. To investigate the association of autonomic symptoms with DAT imaging, we first analyzed whether the frequency of symptoms that suggest autonomic impairment differed between the subgroups. If appropriate, multivariable logistic-regression models were employed next. In these models, DAT uptake was inserted as a continuous variable. The level of statistical significance was set at a p value < 0.05. Calculations were performed with SPSS 18.0 (SPSS Inc., Chicago, IL).

3. Results

The cutoff points for the mild-, moderate-, and severe-reduction groups were 2.20 and 1.75 in the caudate and 0.90 and 0.68 in the putamen, respectively. The demographic and clinical characteristics of the patients in each subgroup according to DAT activity are shown in Table 1. There were significant differences in age at enrollment, age at onset, and the MDS-UPDRS motor score and total score across the subgroups.

The frequency of symptoms that suggest autonomic impairment in each subgroup is presented in Fig. 1. In the classification based on caudate DAT uptake, the severe-reduction group had a higher occurrence of symptoms that suggest gastrointestinal impairment than the moderate-reduction group ($p = 0.024$) but not the mild-reduction group ($p = 0.354$). There were no significant differences in the symptoms that suggest urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual impairments across the groups based on caudate DAT uptake. With respect to putamen DAT uptake, the occurrence of symptoms that suggest urinary impairment was higher in the severe- ($p < 0.001$) and moderate-reduction ($p = 0.015$) groups than in the mild-reduction group, but no significant difference was found between the groups with moderate- and severe-reduction ($p = 0.892$). There were no differences in the other autonomic symptoms between the groups based on putamen DAT uptake.

Based on the results of univariable analyses showing potential correlations of gastrointestinal or urinary impairment with striatal dopaminergic depletion, these domains were further analyzed in multivariable logistic regression models that controlled for age at enrollment, sex, and disease duration. In the models, symptoms that suggest urinary impairment were significantly associated with putamen DAT uptake [adjusted odds ratio (OR) 0.406; 95% confidence interval [CI] 0.203–0.812; $p = 0.011$] but not caudate DAT uptake (adjusted OR 0.697; 95% CI 0.483–1.005; $p = 0.053$). Symptoms that suggest gastrointestinal impairment were not associated with DAT uptake in both the caudate (adjusted OR 0.723; 95% CI 0.436–1.199; $p = 0.209$) and putamen (adjusted OR 1.328; 95% CI 0.554–3.182; $p = 0.525$).

4. Discussion

The current study sought to detect the association between various autonomic symptoms covered by the SCOPA-AUT and striatal dopamine depletion in 418 patients with untreated PD. We identified that a lower level of DAT activity in the putamen but not in the caudate was related to symptoms that suggest urinary impairment in these patients. On the other hand, striatal DAT activities were not associated with symptoms that suggest gastrointestinal, cardiovascular, thermoregulatory, pupillomotor, and sexual impairments. To the best of our knowledge, this is the first report to explore the striatal dopaminergic pathway as being implicated in the pathogenesis of autonomic symptoms in drug-naive PD.

Growing evidence indicates that nigrostriatal dopaminergic fibers have an important role in normal bladder control (Kim and Jeon, 2017), and therefore, their dysfunction can induce urinary symptoms in patients with PD. However, there have been conflicting results regarding which of the striatal subregions is more closely linked with urinary symptoms. Winge et al., 2005 reported that the putamen-to-caudate ratio positively correlated with the Danish Prostate Symptom Score in seven patients with PD who had prominent bladder symptoms, which indicates that the severity of these symptoms may be dependent on the relative degeneration of the caudate. Alternatively, lesions of the putamen in patients with stroke are very closely associated with urinary symptoms (Panicker et al., 2015), which is in line with our findings. However, two previous studies found that the activation pattern in the putamen was maintained during bladder filling both in nine patients with PD who had detrusor overactivity and in 17 young healthy volunteers, suggesting that detrusor overactivity in PD may occur regardless of activation in the putamen (Kitta et al., 2006; Matsuura et al., 2002). We believe that our results are more reliable than those previously obtained because the current study included a much larger number of patients who had not received treatment for PD. Furthermore, adjustment for confounding factors was performed. However, given that the pattern of degeneration moves from a putaminal to a caudate trajectory, we cannot exclude the possibility that urinary symptoms and putaminal dopamine loss are both features of early PD with no pathogenic link to each other. To clarify this issue, further studies are needed to investigate their relationship at various stages of PD.

Other autonomic symptoms were not associated with striatal DAT activity. In fact, the main central autonomic structures affected in PD are the hypothalamus, certain brainstem structures at the pontomesencephalic and bulbopontine levels, and the spinal cord, which are extrastriatal structures (Coon et al., 2018). Thus, it is not surprising that their association was not significant in this study. However, symptoms of cardiovascular and pupillomotor impairments occurred only in a very low number of the patients, suggesting that the association of such symptoms with DAT imaging needs to be investigated at more advanced stages of PD.

This study has several limitations. First, autonomic symptoms were assessed only based on self-report questionnaire scores. The addition of objective assessments of autonomic function should be considered to improve the diagnostic accuracy in further studies. Second, symptoms included in the same autonomic domain of the SCOPA-AUT may have different pathomechanisms, and therefore, our results should be

Table 1
Characteristics of each subgroup according to dopamine transporter (DAT) activity.

	Caudate DAT uptake				Putamen DAT uptake			
	Mild reduction (n = 139)	Moderate reduction (n = 140)	Severe reduction (n = 139)	*p* value	Mild reduction (n = 139)	Moderate reduction (n = 140)	Severe reduction (n = 139)	*p* value
Demographic and clinical data								
Male sex (%)	84 (60)	93 (66)	96 (69)	0.301	89 (64)	89 (64)	95 (68)	0.653
Age at enrollment, years	58.9 (10.4)	62.0 (9.9)	62.8 (8.5)	0.002[a,b]	59.0 (10.7)	61.6 (9.3)	63.1 (8.7)	0.002[b]
Disease duration, years	2.1 (2.3)	2.1 (2.2)	1.8 (1.3)	0.388	1.9 (2.3)	2.0 (2.2)	2.0 (1.4)	0.790
Age at onset, years	57.4 (10.9)	60.3 (10.0)	61.4 (8.5)	0.002[a,b]	57.6 (11.2)	60.0 (9.5)	61.5 (8.8)	0.004[b]
MDS-UPDRS total score	30.2 (11.8)	31.0 (12.3)	35.3 (13.2)	0.001[b,c]	27.4 (11.6)	32.9 (11.0)	36.1 (13.6)	< 0.001[a,b]
MDS-UPDRS motor score	19.4 (8.5)	20.6 (8.9)	22.4 (8.7)	0.015[b]	17.4 (8.2)	22.1 (8.1)	22.9 (9.0)	< 0.001[a,b]
MoCA score	27.4 (2.4)	27.0 (2.1)	27.1 (2.3)	0.270	27.4 (2.4)	27.0 (2.2)	27.0 (2.3)	0.287
Imaging data (striatal binding ratio)								
Caudate DAT uptake	2.6 (0.3)	2.0 (0.1)	1.4 (0.3)	< 0.001[a,b,c]	2.5 (0.4)	2.0 (0.4)	1.5 (0.4)	< 0.001[a,b,c]
Putamen DAT uptake	1.1 (0.3)	0.8 (0.2)	0.6 (0.2)	< 0.001[a,b,c]	1.1 (0.3)	0.8 (0.1)	0.5 (0.1)	< 0.001[a,b,c]

Data are n (%) and the mean (SD).
Bonferroni post-hoc was performed when one-way ANOVA or Pearson χ^2 test reported a p value of < 0.05.
Abbreviations: MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; SD, standard deviation; ANOVA, analysis of variance.
[a] p value < 0.05 by post-hoc comparison between mild and moderate reduction.
[b] p value < 0.05 by post-hoc comparison between mild and severe reduction.
[c] p value < 0.05 by post-hoc comparison between moderate and severe reduction.

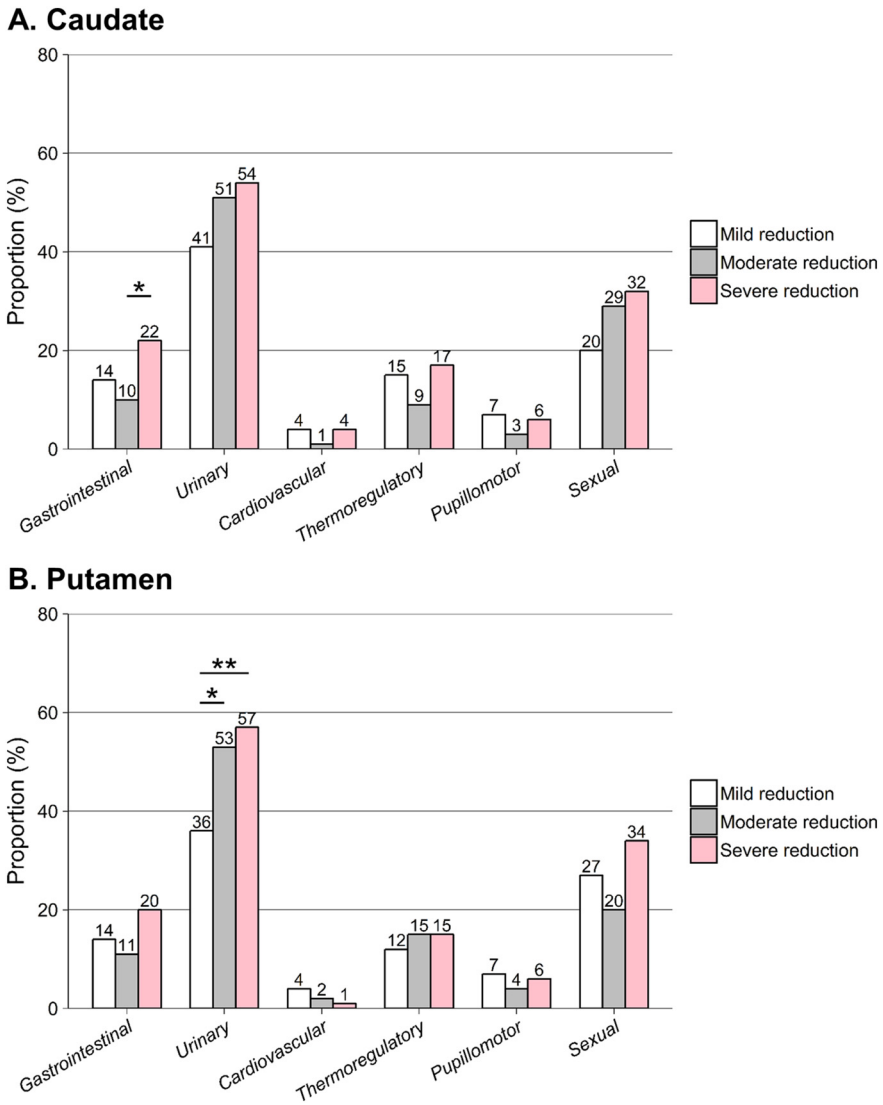

Fig. 1. The frequency of symptoms that suggest autonomic impairment in each subgroup according to dopamine transporter activity.
*$p < 0.05$, **$p < 0.005$.

interpreted with caution. Unfortunately, we could not perform an analysis based on each item of the SCOPA-AUT in this study because the proportion of impairment in each item was mostly low. Third, although our patients had not been treated with dopaminergic drugs, they were not required to stop using other drugs that could affect autonomic function. This might have led to overestimation of autonomic symptoms. Last, this was a cross-sectional study, thereby limiting our ability to determine the relationship between dopaminergic contribution to autonomic dysfunction and disease progression.

In conclusion, we found evidence for a dopaminergic association with urinary symptoms but not with gastrointestinal, cardiovascular, thermoregulatory, pupillomotor and sexual symptoms in patients with drug-naive PD. Moreover, our results suggest that dopaminergic denervation in the putamen but not in the caudate may underlie urinary symptoms in these patients.

Authors' contributions

Dr. R Kim designed the research, acquired and analyzed the data and drafted the manuscript.

Dr. JS Jun designed the research, analyzed the data, and made critical revisions to the manuscript.

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Conflict of interest statement

No conflicting relationship exists for the authors.

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References

Coon, E.A., Cutsforth-Gregory, J.K., Benarroch, E.E., 2018. Neuropathology of autonomic dysfunction in synucleinopathies. Mov. Disord. 33 (3), 349–358.

Dayan, E., Sklerov, M., Browner, N., 2018. Disrupted hypothalamic functional connectivity in patients with PD and autonomic dysfunction. Neurology 90 (23), e2051–e2058.

Forjaz, M.J., Ayala, A., Rodriguez-Blazquez, C., Frades-Payo, B., Martinez-Martin, P., 2010. Assessing autonomic symptoms of Parkinson's disease with the SCOPA-AUT: a new perspective from Rasch analysis. Eur. J. Neurol. 17 (2), 273–279.

Kim, R., Jeon, B., 2017. Nonmotor effects of conventional and transdermal dopaminergic therapies in Parkinson's disease. Int. Rev. Neurobiol. 134, 989–1018.

Kim, R., Lee, J., Kim, Y., Kim, A., Jang, M., Kim, H.J., et al., 2018. Presynaptic striatal dopaminergic depletion predicts the later development of freezing of gait in de novo Parkinson's disease: an analysis of the PPMI cohort. Parkinsonism Relat. Disord. 51, 49–54.

Kitta, T., Kakizaki, H., Furuno, T., Moriya, K., Tanaka, H., Shiga, T., et al., 2006. Brain activation during detrusor overactivity in patients with Parkinson's disease: a positron emission tomography study. J. Urol. 175 (3), 994–998.

Matsuura, S., Kakizaki, H., Mitsui, T., Shiga, T., Tamaki, N., Koyanagi, T., 2002. Human brain region response to distention or cold stimulation of the bladder: a positron emission tomography study. J. Urol. 168 (5), 2035–2039.

Merola, A., Romagnolo, A., Rosso, M., Suri, R., Berndt, Z., Maule, S., et al., 2018. Autonomic dysfunction in Parkinson's disease: a prospective cohort study. Mov. Disord. 33 (3), 391–397.

Muller, B., Larsen, J.P., Wentzel-Larsen, T., Skeie, G.O., Tysnes, O.B., 2011. Autonomic and sensory symptoms and signs in incident, untreated Parkinson's disease: frequent but mild. Mov. Disord. 26 (1), 65–72.

Panicker, J.N., Fowler, C.J., Kessler, T.M., 2015. Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. Lancet Neurol. 14 (7), 720–732.

Sakakibara, R., Shinotoh, H., Uchiyama, T., Yoshiyama, M., Hattori, T., Yamanishi, T., 2001. SPECT imaging of the dopamine transporter with [(123)I]-beta-CIT reveals marked decline of nigrostriatal dopaminergic function in Parkinson's disease with urinary dysfunction. J. Neurol. Sci. 187 (1–2), 55–59.

Winge, K., Friberg, L., Werdelin, L., Nielsen, K.K., Stimpel, H., 2005. Relationship between nigrostriatal dopaminergic degeneration, urinary symptoms, and bladder control in Parkinson's disease. Eur. J. Neurol. 12 (11), 842–850.