Differential roles of regional enlarged perivascular spaces in cognition and neuropsychiatric burden in drug naïve Parkinson's disease

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Differential roles of regional enlarged perivascular spaces in cognition and neuropsychiatric burden in drug naïve Parkinson's disease

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ABSTRACT

Differential roles of regional enlarged perivascular spaces in cognition and neuropsychiatric burden in drug naive Parkinson's disease

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Background: Despite growing body of evidence supporting the potential role of enlarged perivascular space (EPVS) in Parkinson's disease (PD), the relationship among regional EPVS burden, cognition and neuropsychiatric symptoms remains open to debate. Herein, we investigated the regional EPVS burden and their association with cognition and NPS in a relatively large cohort of drug-naïve PD population.

Methods: Regional EPVS burden was visually rated on T2-weighted images in 480 drug-naïve PD patients (cognitively unimpaired, n=123; mild cognitive impairment [MCI], n=291; dementia, n=66) who underwent magnetic resonance imaging (MRI), dopamine transporter (DAT) scan, neuropsychological battery, and Neuropsychiatric Inventory Questionnaire (NPI-Q) at initial assessment. T-EPVS and BG-EPVS were defined as "high-degree" when the counts in any hemisphere were >10, while the cutoff for CS-EPVS was >20. Cognitive performance and the burden of neuropsychiatric symptom along with vascular risk factors, small vessel disease (SVD) imaging markers and DAT availability were compared according to regional EPVS burden.

Results: The proportion of high-degree T-EPVS (P for trend <0.001) and BG-EPVS (P for trend = 0.001) had an increasing trend throughout the cognitive spectrum in the order of worsening of cognition. High-degree BG-EPVS group were likely to have higher systemic vascular comorbidities (hypertension and cardiac disease), lower cognitive performance (language and visual memory domain), higher SVD burden (white matter hyperintensity, lacune, cerebral microbleeds) compared to low-degree BG-EPVS group. High-degree T-EPVS group had a tendency to show higher neuropsychiatric burden in terms of decreased motivation (P=0.004), affective dysregulation (P<0.001), and impulse dyscontrol (P<0.001)

compared to low-degree T-EPVS group. Meanwhile, increased burden of CS-EPVS had older age and comorbid hypertension, without exhibiting any difference in cognition or neuropsychiatric symptoms.

Conclusions: BG-EPVS and T-EPVS appears to exert differential effects on cognition and neuropsychiatric symptoms in patients with PD. Investigating the EPVS profile in distinct anatomical regions may serve as useful imaging biomarkers for disentangling the heterogeneity of PD.

Key words : Parkinson disease, glymphatic system, cognitive dysfunction, apathy, affective symptoms

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I. INTRODUCTION

Perivascular spaces (PVS) are fluid-filled spaces located along cerebral small vessels penetrating the brain which plays a major role in the clearance of fluid and solutes throughout the central nervous system.[1] While PVS are not detected on magnetic resonance imaging (MRI) in normal physiological conditions, PVS dilates under glymphatic dysfunction to an extent that could be traced upon MRI (i.e., enlarged PVS [EPVS]).[1-3] Along with arterial/arteriolar stiffness (i.e., vascular etiology), retrograde PVS dilation subsequent to abnormal protein aggregation clogging up the upstream are widely accepted as one of major pathophysiological mechanisms for EPVS, shedding light on various neurodegenerative disorders.[3] With recent evidence suggesting the potential role of dysfunctional perivascular clearance of alpha-synuclein in Parkinson's disease (PD)[4-7] which is even observed in the prodromal stage (i.e., rapid eye movement sleep behavior disorder)[7], EPVS has recently gained attention in PD population.

Despite growing body of evidence supporting the contribution of perivascular impairment in development and progression of PD, there exists several areas of uncertainty that should be further elucidated. First, most of the previous studies have focused on EPVS located in the basal ganglia (BG-EPVS) due to its close spatial relationship to nigrostriatal pathway[8-11], but the prevalence, risk factors, and clinical implication of EPVS located elsewhere in PD population remains obscure. Given that the etiologies underlying EPVS tend to differ across their anatomical locations[12-14], comprehensive investigation for regional EPVS burden other than BG-EPVS (e.g., EPVS located in centrum semiovale [CS-EPVS][12, 13] or temporal lobe [T-EPVS][14]) of EPVS may enhance our understanding the role EPVS in PD pathophysiology. Second, although the association between EPVS and motor symptoms in PD has been increasingly reported[9-11], the contribution of EPVS burden in

cognitive and neuropsychiatric symptoms (NPS) are not yet clearly understood. Lastly, it is somewhat unclear whether EPVS indeed have clinical consequences by itself or whether the association with clinical manifestations are attributable to other small vessel disease (SVD) markers which commonly coexist with EPVS.[15-17]

To address the aforementioned gap of knowledge, we investigated the regional EPVS burden and their association with cognition and NPS in a relatively large cohort of drug-naïve PD population. Specifically, the objectives for our study was (1) to explore the prevalence of regional EPVS burden (T-EPVS, CS-EPVS, and BG-EPVS) throughout the cognitive spectrum in drug naive PD, (2) to assess the difference in clinical, DAT availability, vascular risk factors, and burden of other SVD markers according to the burden of regional EPVS, (3) to evaluate the association between regional EPVS burden and measures of cognitive/neuropsychiatric symptoms. Additionally, we further investigated whether the regional EPVS burden exert an independent effect on cognition and neuropsychiatric symptoms, or the effect is indirectly mediated by other SVD markers.

II. METHODS

1. Study population

A total of 480 consecutive patients with anti-parkinsonian drug-naïve PD who visited the movement clinic at Severance Hospital from June 2015 to December 2020 were included in this study. Diagnosis of PD was made in accordance with the clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank. All patients underwent 18F N-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane positron emission tomography (18F-FP-CIT PET) scans, brain MRI scans, and standardized neuropsychological assessment along with neuropsychiatric inventory questionnaire (NPI-Q) at baseline. All patients included in this study exhibited decreased uptake on 18F-FP-CIT PET in the posterior putamen, and patients responded to dopaminergic medication during the follow-up period (2 years at least). Patients with following criteria was excluded from our study: (1) previous history of other neurologic disorders including epilepsy or stroke, (2) previous history of traumatic brain injury or unexplained structural brain lesions observed in MRI scans, (3) patients who did not exhibit responsiveness to anti-parkinsonian therapy, and (4) patients who exhibited features consistent with atypical parkinsonian syndrome during the follow-up period (>2 years).

Cognitive status of our study participants were determined according to the Movement Disorder Society Task Force guidelines[18]: PD with intact cognition (PD-SCI), PD with mild cognitive impairment (PD-MCI), and PD dementia (PDD). Parkinsonian motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) prior to initiation of anti-parkinsonian therapy. The motor subtypes (i.e., tremor-dominant, postural instability/gait difficulty, or indeterminate) were determined based on UPDRS scores based on the criteria described previously.[19]

This study was approved by the institutional review board of Yonsei University Severance Hospital. Considering the nature of retrospective study design and informed consent from participants was waived in this study.

2. MR and PET image acquisition

Brain MRI scans were acquired using a 3T scanner (Achieva; Philips Medical Systems, Best, the Netherlands) with a 32-channel receiver array head coil. The imaging protocol included T2-weighted images (repetition time [TR]/echo time [TE], 2,800–3,000/80–100 ms; section thickness, 5 mm; matrix, 256 × 256), fluid-attenuated inversion recovery (FLAIR) images (TR/TE, 9,000–10,000/110–125 ms; section thickness, 5 mm; matrix, 256 × 256), and T2*-weighted gradient echo images (TR/TE, 500–1,000/15–25 ms; slice thickness, 5 mm; matrix, 256 × 256).

FP-CIT PET scans were acquired using a Discovery 600 system (GE Healthcare; Milwaukee, WI, USA). After fasting for at least 6 hours, the patients were intravenously injected with 5 mCi (185 MBq) of 18F-FP-CIT. PET images were acquired for 20 min in three-dimension 90 min after the injection. The spiral CT scan was performed with 0.8 seconds per rotation at 120 kilovolt peak (kVp), 10mA, 3.75mm slice thickness, 0.625mm collimation, and 9.375mm table feed per rotation. Images were reconstructed using the ordered subset expectation maximization algorithm with 4 iterations and 32 subsets. Gaussian filter with 4-mm full-width at half-maximum was applied to reconstructed PET images, which were 256 x 256 matrices with 0.98-mm pixel and 0.98-mm slice thickness.

3. Quantitative analysis of PET data

In quantitative analyses of 18F-FP-CIT PET dopamine transporter (DAT) availability, statistical parametric mapping 12 (SPM12; Wellcome Trust Centre for Neuroimaging,

London, UK) and in-house software implemented in MATLAB R2021a (MathWorks, Natick, MA) were employed. Image processing was performed by following the methodology described previously.[20, 21] Briefly, PET images were coregistered to their corresponding MRI and spatially normalized by using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra toolbox. In achieving the specific binding ratio (SBR), difference in DAT uptake values between each voxel in the striatum and the uptake in the reference region (cerebellar gray matter) were divided by the uptake in the reference region. Regional SBR values were obtained by overlaying in-house volume-of-interest (VOI) template for whole striatum, caudate (whole, anterior and posterior caudate), and putamen (whole, anterior and posterior putamen).

4. Neuropsychological assessment

In determining the cognitive status and assessing the cognitive performance of the participants a standardized neuropsychological battery (Seoul Neuropsychological Screening Battery) along with Korean version of the Mini-Mental State Examination (MMSE) were performed. This neuropsychological battery provides raw scores and standardized z-scores based on age-/education-matched norms for following subtests: digit span forward, digit span backward, Stroop color-reading test for attention and working memory domain; the Korean version of the Boston Naming Test for language domain; Rey-Osterrieth Complex Figure Test for visuospatial domain; immediate, 20-minute delayed recall, and recognition of Rey-Osterrieth Complex Figure Test for visual memory; immediate, 20-minute delayed recall, recognition of Seoul Verbal Learning Test for verbal memory domain; and phonemic and semantic Controlled Oral Word Association Test for frontal/executive domain. A composite score for each domain was calculated for each cognitive domain by dividing the sum of z-scores by the number of tests.

5. Neuropsychiatric symptoms

Presence, frequency and severity of NPS of the participants were assessed based on the Korean version of neuropsychiatric inventory (NPI) questionnaire[22], which assess the behavioral and psychological symptoms with 12 items as follows: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior

disturbances, and appetite and eating changes. The frequency (0=absent, 1=less than once per week, 2=about once per week, 3=several times a week, 4=daily or continuously) and severity (0=absent, 1=mild, 2=moderate, 3=severe) for each symptom are rated retrospectively based on the observations within the preceding 4 weeks. Composite NPI-Q score is calculated by adding up the scores of 12 items (NPI-Q-12 total score) or 10 items excluding sleep and nighttime behavior disturbances, and appetite and eating changes (NPI-Q-10 total score). "Clinically significant" symptoms for each items were defined as NPI score≥4.[23]

In order to minimize the issue of multiple comparison, composite subscores outlined by the research criteria for mild behavior impairment (MBI)[24] based on NPI-Q 10 items using a modified reference range of 4 weeks[25] were produced for the following five behavioral domains: decreased motivation (apathy/indifference), affective dysregulation (depression/dysphoria, anxiety, and elation/euphoria), impulse dyscontrol (agitation/aggression, irritability/lability, and aberrant motor behavior),social inappropriateness (disinhibition), and abnormal perception or thought content (delusions and hallucinations).

6. EPVS

EPVS was evaluated based on the Standards for Reporting Vascular Changes on Neuroimaging criteria(STRIVE) [26], where EPVS is characterized by round or ovoid shape in axial images with a diameter of less than 3mm and does not have a T2 hyperintense rim around the space on T2-weighted imaging. EPVS was manually counted on axial T2-weighted MRI by 2 separate neurologists (H.K.Na and S.J.Chung) blinded to the clinical information during counting. Three different regions: basal ganglia, centrum semiovale, and temporal lobe were visually rated. EPVS were counted in bilateral hemispheres and higher counts in one hemisphere were used. BG-EPVS and CS-EPVS were rated using a widely approved visual rating scale (0 = no EPVS, 1 = 1-10 EPVS, 2 = 11-20 EPVS, 3 = 21-40 EPVS, 4 = 40< EPVS). The degree of EPVS burden was then dichotomized into high-degree and low-degree (Cut-off points n>20 for CS-EPVS, n>10 for T-EPVS and BG-EPVS). Referring from a previous study [14], visual rating of T-EPVS was done at 3 axial slices: level of superior colliculus, inferior colliculus, and rostral pons. The T-EPVS was classified as follows: 0 = no T-EPVS, 1 = 1-10 T-EPVS, 2 = 11-20 T-EPVS, 3 = 20< T-

EPVS. In T-EPVS, the EPVS burden was dichotomized using the cutoff value of 10. Representative examples of EPVS grading by regions are shown in Figure 1.

The interrater reliability (ICC) was excellent for BG-EPVS, CS-EPVS, and T-EPVS (0.885). When EPVS degree were discordant, decision was made through consensus discussion.

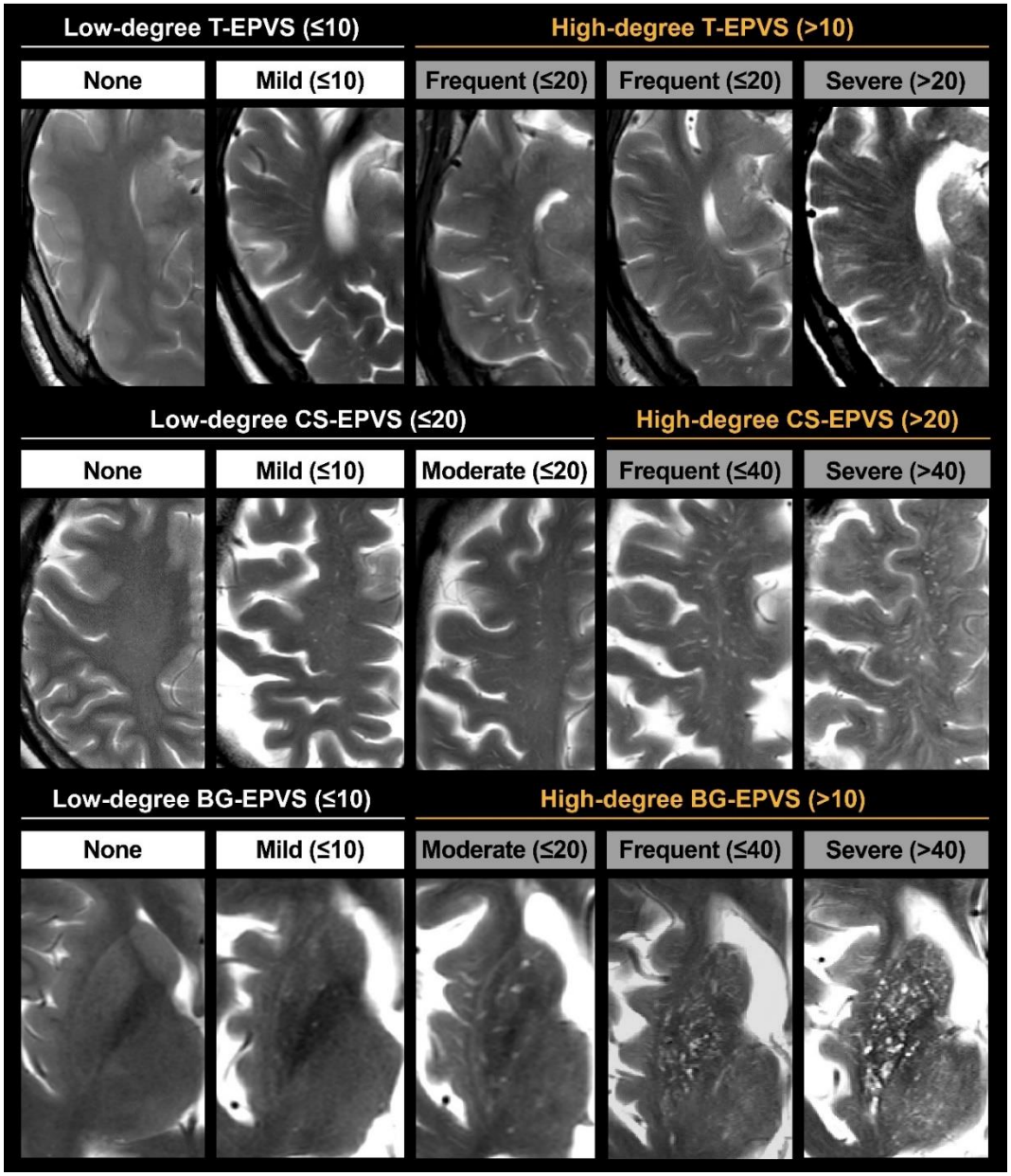

Figure 1. Examples of regional EPVS in three anatomical locations. Representative images of EPVS in the temporal lobe (T-EPVS), centrum semiovale (CS-EPVS), and basal

ganglia (BG-EPVS) according to their severity are presented. High-degree EPVS was defined by using cut-off point of 10 in T-EPVS and BG-EPVS, while cut-off point of 20 was used in CS-EPVS.

7. Small vessel disease burden: WMH, lacunes, and cerebral microbleeds

Lacunes and white matter hyperintensity of presumed vascular origin (WMH) were evaluated based on the Standards for Reporting Vascular Changes on Neuroimaging criteria (STRIVE) [26]. Lacunes are differentiated with PVS by the size, where lacunes are between 3mm and 15mm in diameter. White matter hyperintensity is assessed in T2 FLAIR images and graded in accordance with Fazekas scale. Periventricular WMH areas were graded as P1 (cap and band <5mm), P2 (5mm cap or band <10mm), and P3 (10mm ≤ cap or band); deep WMH areas were graded as D1 (maximum diameter of deep white matter lesion <10mm), D2 (10mm ≤ lesion <25mm), and D3 (≥ 25mm). Cerebral microbleeds (CMB) are small round or oval shaped lesions visualized as low signal in T2-weighted gradient echo (GRE) image. CMB was classified as deep and lobar depending on the location of CMB. Lobar CMB included cortical and subcortical regions and deep CMB included the basal ganglia, thalamus, internal/external capsule, and the corpus callosum. WMH grading, presence of lacune, presence of lobar/deep CMBs were manually rated by 2 neurologists (H.K.Na and S.J.Chung) blinded to clinical information.

8. Statistical analysis

In comparing the demographic, clinical, and imaging characteristics between the two groups (high-degree versus low-degree), continuous variables were compared by using t-test and Mann-Whitney U test according to their distributions. When comparing continuous variables more than two groups, analysis of variance followed by Least Significant Difference post hoc tests or Kruskal Wallis test followed by Dunn's post-hoc test was used. Chi-square or Fisher's exact test was used for comparing categorical variables among groups.

Group difference in DAT availability of each striatal subregion was analyzed by using analysis of covariance (ANCOVA) adjusting for age, sex, education years, disease duration, motor subtypes, cognitive status, MMSE scores, DWMH, PWMH, presence of lacune were used as covariates. When comparing composite scores for each cognition domain according

to EPVS burden, two models of ANCOVA was performed to test the effect of SVD markers other than EPVS. In Model 1 (a model without including SVD markers), covariates included age, sex, education years, cognitive status, Mini-Mental State Examination (MMSE) scores, and DAT availability in caudate and posterior putamen, while deep/periventricular WMH burden and presence of launces along with covariates used in Model 1 were used in Model 2 (a model controlling for other SVD markers). In comparing the severity of NPS, similar analyses using the same covariates were performed, but non-parametric ANCOVA based on permutation (testing against shuffled data with n = 1000 permutations) was used considering the distribution of NPS scores. In order to control issues of multiple comparison, false discovery rate (FDR) method was applied.

In comparing the frequency of NPS in terms of 12-item version NPI-Q and NPS subdomains defined by MBI criteria chi-square tests were used for comparisons. In order to test whether regional EPVS serve as a predictor for each behavioral domain of NPS, multivariate logistic regression analysis was performed. Three regional EPVS was entered in the multivariate model, using age, sex, education years, cognitive status, MMSE scores, DAT availability in the caudate and putamen as covariates.

Lastly, mediation analyses were performed as supplementary analyses in order to confirm whether the association between regional EPVS burden and clinical measures for cognition and NPS are mediated by other SVD markers only in those where EPVS burden, SVD markers, and clinical measures reveal significant correlations using PROCESS MACRO package version 4.1 in R. Covariates used in this analyses were age, sex, education years, cognitive status, MMSE scores, DAT availability in caudate and posterior putamen, and SVD markers except for variables used as the mediator.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA) and R software package (version 4.1, http://www.r-project.org/). Throughout the analyses, $P<0.05$ or FDR-corrected P value < 0.05 was considered to be statistically significant.

III. RESULTS

1. Clinical and imaging characteristics of study participants

The clinical and imaging characteristics of the study participants are presented in Table 1. Among 480 patients with PD (mean age, 71.3±8.5; female, 50.2%), 133 had moderate-

to-severe DWMH (27.7%), 159 had moderate-to-severe PWMH (33.1%), and lacune was present in 102 patients (21.3%). In terms of regional EPVS burden, proportion of high-degree T-EPVS, CS-EPVS, and BG-EPVS were 180 (37.5%), 365 (76.0%), and 129 (26.9%), respectively.

At the time of diagnosis, 123 patients had intact cognition (PD-SCI, 25.6%), 291 patients were PD-MCI (60.6%), and 66 patients were determined as PDD (13.8%). The proportion of high-degree T-EPVS (P for trend <0.001) and BG-EPVS (P for trend = 0.001) had an increasing trend throughout the cognitive spectrum in the order of worsening of cognition (Figure 2), while the trend was only marginal in CS-EPVS (P for trend = 0.050).

Table 1. Clinical and imaging characteristics of the study population

Characteristics	
Clinical factors	
Age, years	71.27±8.54
Sex, male:female	239:241
Education, years	10.06±5.10
Disease duration, years	1.62±1.72
Motor subtypes	
Tremor-dominant, n (%)	194 (40.42)
Intermediate, n (%)	76 (15.83)
PIGD, n (%)	210 (43.75)
Cognitive status	
Intact cognition, n (%)	123 (25.6)
Mild cognitive impairment, n (%)	291 (60.6)
Dementia, n (%)	66 (13.8)
UPDRS Part III	21.03±9.07
Mini-Mental State Examination score	25.77±3.5
Vascular risk factors	
Body-mass index	24.13±3.14
Hypertension, n (%)	248 (51.67)
Diabetes mellitus, n (%)	129 (26.88)
Dyslipidemia, n (%)	152 (31.67)
Cardiac disease, n (%)	63 (13.13)
SVD imaging markers	
High-degree T-EPVS, n (%)	180 (37.50)
High-degree CS-EPVS, n (%)	365 (76.04)
High-degree BG-EPVS, n (%)	257 (53.54)
WMH grade≥2, n (%)	137 (28.54)
DWMH grade≥2, n (%)	133 (27.71)
PWMH grade≥2, n (%)	159 (33.13)
Presence of lacune, n (%)	102 (21.25)
Presence of lobar CMB, n (%)	58 (12.08)

Presence of deep CMB, n (%)	28 (5.83)

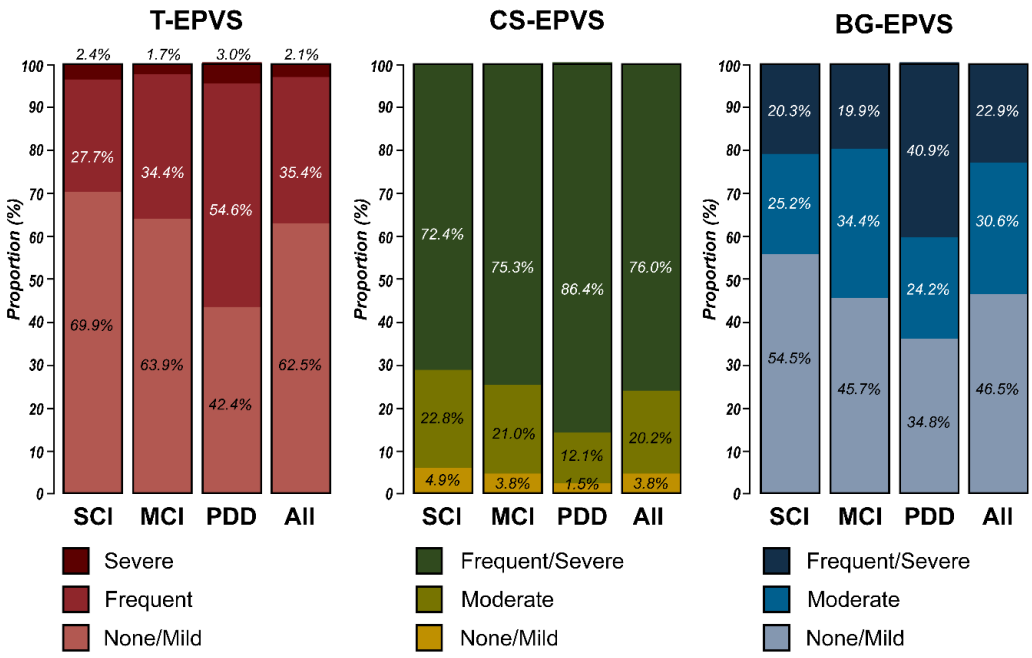

Figure 2. EPVS burden in three anatomical regions according to cognitive status. In each anatomical regions of EPVS (T-EPVS, CS-EPVS, and BG-EPVS) and cognitive status (SCI, MCI, and PDD), the severity of EPVS is shown in proportions.

2. Factors associated with regional EPVS burden

The demographic, clinical, and imaging characteristics according to the regional EPVS burden are in Table 2. In all three regional EPVS, high-degree EPVS group had older age compared to low-degree EPVS group. Disease duration did not differ between high-degree EPVS and low-degree EPVS in all three regions. High-degree T-EPVS and BG-EPVS groups had higher UPDRS III score than low-degree groups. In BG-EPVS, high-degree group had more PIGD motor subtype than low-degree group (49.81% versus 36.77%, P = 0.010). The cognitive status differed significantly in only T-EPVS and BG-EPVS, both showing higher proportion of PDD in high-degree group.

High-degree BG-EPVS group had more hypertension (61.48% versus 40.36%, P <0.001) and more cardiac disease history (17.9% versus 7.62%, P = 0.001) than low-degree group. High-degree CS-EPVS had more hypertension (54.52% versus 42.61%, P = 0.026) than low-degree group. In all three regions of EPVS, BMI, diabetes mellitus, and dyslipidemia

history did not show significant difference between high-degree and low-degree groups. In DAT scan, there were no significant differences of DAT availability between high-degree and low-degree EPVS groups in all three regions. The proportion of Fazekas grade≥2 (40.47% versus 14.80%, P <0.001), deep WMH grade≥2 (39.3% versus 14.35%, P <0.001), and periventricular WMH grade≥2 (48.25% versus 15.70%, P <0.001) were significantly higher in high-degree BG-EPVS group than low-degree group. Also, high-degree BG-EPVS group had more presence of lacune (30.74% versus 10.31%, P <0.001), lobar CMB (16.73% versus 6.73%, P = 0.001), deep CMB (9.73% versus 1.35%, P <0.001) in brain MRI than low-degree group. In contrast, the degree of T-EPVS and CS-EPVS did not show any significant relationship with WMH grade and lacune.

3. Cognitive performance according to regional EPVS burden

Without considering SVD markers other than EPVS (Model 1), PD patients with high-degree BG-EPVS exhibited worse performance in language (P=0.006), visual memory (P=0.006), and frontal/executive domain (P=0.023) compared to those with low-degree BG-EPVS, which remained significant even after controlling for multiple comparison. When further adjusting for other SVD markers (Model 2), the difference in the frontal/executive dysfunction with regards to BG-EPVS burden did not reach statistical significance (P=0.165).

Table 2. Demographic and imaging characteristics according to regional EPVS burden

	T-EPVS			CS-EPVS			BG-EPVS		
	Low-degree (n=300)	High-degree (n=180)	P-value	Low-degree (n=115)	High-degree (n=365)	P-value	Low-degree (n=223)	High-degree (n=257)	P-value
Clinical factors									
Age, years	69.69±8.58	73.90±7.80	**<0.001**	69.17±9.92	71.93±7.95	**0.007**	67.55±8.88	74.5±6.74	**<0.001**
Onset age, years	68.24±8.55	72.01±8.00	**<0.001**	67.73±9.96	70.26±7.95	**0.014**	66.07±8.9	72.76±6.83	**<0.001**
Sex, male:female	159:141	80:100	0.070	58:57	181:184	0.874	108:115	131:126	0.578
Education, years	10.38±4.99	9.52±5.25	0.065	11.00±5.30	9.76±5.01	**0.015**	10.59±4.94	9.60±5.20	**0.029**
Disease duration, years	1.45±1.43	1.89±2.10	0.244	1.44±1.35	1.67±1.83	0.968	1.47±1.51	1.74±1.89	0.661
UPDRS Part III score	20.31±8.34	22.23±10.07	**0.032**	20.38±9.16	21.23±9.04	0.381	19.65±8.55	22.23±9.35	**0.002**
MMSE score	26.22±3.31	25.01±3.69	**<0.001**	26.23±3.41	25.62±3.52	0.108	26.47±3.07	25.16±3.74	**<0.001**
Motor subtypes, n (%)			0.807			0.942			**0.010**
Tremor-dominant subtype	123 (41.00)	71 (39.44)		45 (39.13)	149 (40.82)		105 (47.09)	89 (34.63)	
Indeterminate subtype	45 (15.00)	31 (17.22)		19 (16.52)	57 (15.62)		36 (16.14)	40 (15.56)	
PIGD subtype	132 (44.00)	78 (43.33)		51 (44.35)	159 (43.56)		82 (36.77)	128 (49.81)	
Cognitive status, n (%)			**<0.001**			0.087			**0.033**
PD-SCI	86 (28.67)	37 (20.56)		34 (29.57)	89 (24.38)		67 (30.04)	56 (21.79)	
PD-MCI	186 (62.00)	105 (58.33)		72 (62.60)	219 (60.00)		133 (59.64)	158 (61.48)	
PDD	28 (9.33)	38 (21.11)		9 (7.83)	57 (15.62)		23 (10.31)	43 (16.73)	
Vascular risk factors									
Body-mass index	24.33±3.09	23.8±3.19	0.074	24.53±3.46	24.01±3.02	0.121	24.2±3.13	24.07±3.15	0.630
Hypertension, n (%)	148 (49.33)	100 (55.56)	0.187	49 (42.61)	199 (54.52)	**0.026**	90 (40.36)	158 (61.48)	**<0.001**
Diabetes mellitus, n (%)	79 (26.33)	50 (27.78)	0.730	32 (27.83)	97 (26.58)	0.792	54 (24.22)	75 (29.18)	0.221
Dyslipidemia, n (%)	97 (32.33)	55 (30.56)	0.685	37 (32.17)	115 (31.51)	0.893	68 (30.49)	84 (32.68)	0.607
Cardiac disease, n (%)	33 (11.00)	30 (16.67)	0.075	17 (14.78)	46 (12.6)	0.546	17 (7.62)	46 (17.9)	**0.001**
DAT availability									
Whole striatum	2.59±0.75	2.55±0.87	0.525	2.61±0.69	2.56±0.83	0.741	2.58±0.74	2.57±0.85	0.502
Anterior caudate	2.72±0.84	2.63±0.88	0.935	2.77±0.86	2.66±0.85	0.646	2.78±0.87	2.60±0.84	0.754
Posterior caudate	1.32±0.49	1.26±0.52	0.881	1.34±0.51	1.28±0.5	0.982	1.38±0.53	1.22±0.47	0.902
Anterior putamen	3.24±0.95	3.21±1.09	0.321	3.26±0.85	3.22±1.05	0.545	3.18±0.90	3.27±1.09	0.457
Posterior putamen	2.18±0.86	2.21±1.00	0.384	2.15±0.77	2.21±0.95	0.841	2.10±0.76	2.27±1.02	0.318

SVD imaging markers									
WMH burden, Fazekas≥2, n (%)	78 (26.00)	59 (32.78)	0.111	78 (26.00)	59 (32.78)	0.365	33 (14.80)	104 (40.47)	**<0.001**
DWMH burden, grade≥2, n (%)	75 (25.00)	58 (32.22)	0.087	75 (25.00)	58 (32.22)	0.356	32 (14.35)	101 (39.3)	**<0.001**
PWMH burden, grade≥2, n (%)	94 (31.33)	65 (36.11)	0.282	94 (31.33)	65 (36.11)	0.247	35 (15.70)	124 (48.25)	**<0.001**
Presence of lacune, n (%)	59 (19.67)	43 (23.89)	0.274	59 (19.67)	43 (23.89)	0.683	23 (10.31)	79 (30.74)	**<0.001**
Presence of lobar CMB, n (%)	30 (10.00)	28 (15.56)	0.071	30 (10.00)	28 (15.56)	0.747	15 (6.73)	43 (16.73)	**0.001**
Presence of deep CMB, n (%)	17 (5.67)	11 (6.11)	>0.999	17 (5.67)	11 (6.11)	0.246	3 (1.35)	25 (9.73)	**<0.001**

Table 3. Cognitive performance and neuropsychiatric burden according to regional EPVS burden

	T-EPVS				CS-EPVS				BG-EPVS			
	Low-degree (n=300)	High-degree (n=180)	P-value Model 1	P-value Model 2	Low-degree (n=115)	High-degree (n=365)	P-value Model 1	P-value Model 2	Low-degree (n=223)	High-degree (n=257)	P-value Model 1	P-value Model 2
Cognitive performance												
Attention domain	-0.43±0.87	-0.66±0.91	0.273	0.359	-0.47±0.86	-0.53±0.90	0.894	0.548	-0.38±0.89	-0.64±0.88	0.104	0.240
Language domain	-0.27±1.19	-0.58±1.32	0.245	0.396	-0.30±1.14	-0.41±1.28	0.319	0.407	-0.22±1.18	-0.53±1.29	**0.006**	**0.013**
Visuospatial domain	-0.56±1.61	-1.04±2.14	0.284	0.245	-0.63±1.68	-0.78±1.89	0.770	0.828	-0.52±1.42	-0.93±2.12	0.101	0.100
Verbal memory domain	-0.41±1.12	-0.64±1.17	0.100	0.122	-0.34±1.18	-0.55±1.13	0.106	0.153	-0.41±1.14	-0.57±1.14	0.561	0.969
Visual memory domain	-0.34±0.97	-0.59±0.98	0.600	0.663	-0.33±0.94	-0.47±0.99	0.392	0.598	-0.24±0.97	-0.61±0.96	**0.006**	**0.009**
Frontal/executive domain	-0.42±0.82	-0.69±0.86	**0.035**	**0.039**	-0.42±0.79	-0.55±0.86	0.174	0.329	-0.39±0.81	-0.63±0.86	**0.023**	0.165

NPS burden												
NPI-Q 10-item total score	2.13±5.28	6.72±10.36	**<0.001**	**<0.001**	3.11±8.64	4.08±7.65	0.680	0.842	3.01±6.76	4.58±8.72	0.248	0.220
NPI-Q-12-item total score	4.05±7.24	10.54±13.85	**<0.001**	**<0.001**	4.97±10.76	6.96±10.65	0.280	0.371	5.12±8.79	7.67±11.99	0.068	0.057
NPS subdomain score												
Decreased motivation	0.61±1.78	1.35±2.36	**0.004**	**0.006**	0.64±1.92	0.96±2.08	0.395	0.481	0.83±2.04	0.93±2.06	0.658	0.736
Affective dysregulation	0.88±2.13	2.36±3.53	**<0.001**	**<0.001**	1.14±2.66	1.53±2.88	0.584	0.746	1.11±2.67	1.71±2.94	0.159	0.113
Impulse dyscontrol	0.43±1.67	1.74±4.29	**<0.001**	**<0.001**	0.77±3.05	0.98±3.00	0.850	0.901	0.66±2.18	1.15±3.56	0.268	0.321
Social inappropriateness	0.09±0.62	0.37±1.63	0.139	0.243	0.23±1.36	0.19±1.03	0.670	0.630	0.08±0.61	0.30±1.41	**0.015**	**0.031**
Abnormal perception	0.12±1.04	0.88±3.27	0.061	0.131	0.34±2.50	0.43±2.09	0.920	0.750	0.33±2.04	0.48±2.31	0.845	0.998

In secondary path analyses, high-degree BG-EPVS directly affected language and visual memory dysfunction, while the effects were also partially mediated WMH burden (Figure 3A-B). In the frontal/executive domain, however, the effect of BG-EPVS on cognitive performance was completely mediated by WMH burden (Figure 3C).

In both models with and without adjustment for SVD markers other than EPVS, high-degree T-EPVS group showed lower z-score in the frontal/executive domain compared to low-degree T-EPVS group (P=0.035 in Model 1; P=0.039 in Model 2), but the significance did not survive after multiple comparison correction (FDR-corrected P=0.234).

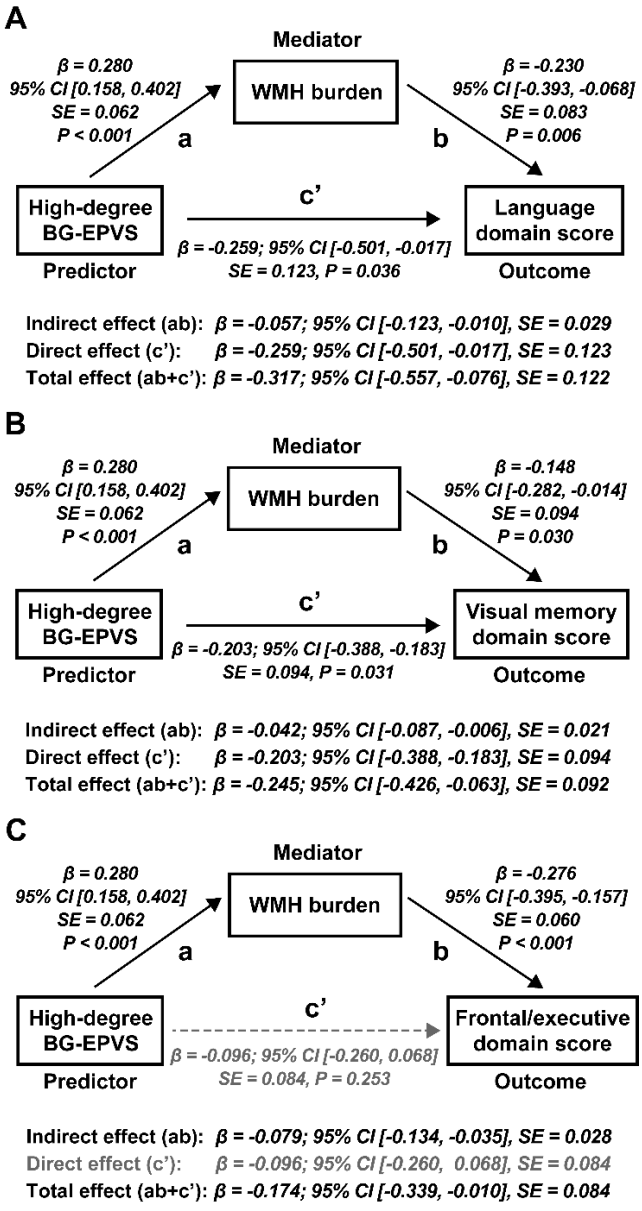

Figure 3. Mediation effect of BG-EPVS on cognitive performance. In cognitive domains that revealed significant association with BG-EPVS burden, path analyses were performed to investigate whether the effects of EPVS were mediated by other SVD markers. Effect of BG-EPVS on language (A) and visual memory (B) was partially mediated by white matter hyperintensity (WMH), while the effect on frontal/executive domain was completely mediated by WMH burden. Significant paths are presented in solid lines, while insignificant paths are presented as dashed lines. Abbreviations: BG-EPVS=enlarged perivascular space in the basal ganglia, CI=confidence interval, SE=standard error

4. Neuropsychiatric symptom according to regional EPVS burden

Prevalence of NPS of each behavioral domain in our study population were as follows: affective dysregulation (37.3%), decreased motivation (25.6%), impulse dyscontrol (17.7%), decreased motivation (25.6%),and social inappropriateness (4.8%).

Prevalence of NPS according to regional EPVS burden is presented in Figure 4. T-EPVS group revealed higher prevalence of NPS in all five behavioral domains compared to low-degree group. In multivariate logistic regression (Table 4), high-degree T-EPVS was significantly associated with presence of decreased motivation (Odd ratio [OR]: 2.065, 95% confidence interval [CI]: 1.277-3.339), affective dysregulation (OR: 2.444, 95% CI: 1.576-3.791), impulse dyscontrol (OR: 3.266, 95% CI: 1.841-5.794), and abnormal perception (OR: 3.763, 95%: 1.526-9.281), while the association with social inappropriateness was no longer significant (OR: 2.601, 95% CI: 0.943-7.173). Although high-degree CS-EPVS showed higher prevalence of decreased motivation (27.9% versus 18.3%, P=0.038) and affective dysregulation (40.8% versus 26.1%) in univariate analyses, the association did not survive in the multivariate model. Similarly, the association between high-degree BG-EPVS and NPS were not significant in multivariate logistic regression models, even though high-degree BG-EPVS tended to reveal higher prevalence in terms of affective dysregulation (42.8% versus 30.9%) and social inappropriateness (7.0% versus 2.2%) in univariate analyses.

In all three regional EPVS, affective dysregulation was more prevalent in patients with high EPVS burden compared to those with low EPVS burden in common. Patients with high EPVS burden in the temporal lobe (36.7% versus 19.0%, P<0.001) and centrum semiovale (27.9% versus 18.3%, P=0.038) were more likely to show decreased motivation.

Meanwhile, patients with higher burden of T-EPVS (7.0% vs 2.2%) and BG-EPVS (7.0% vs 2.2%) had a higher tendency to suffer from social inappropriateness.

Table 4. Multivariate logistic regression model for predictors of neuropsychiatric symptoms

	Adjusted OR (95% CI)	P-value
Decreased motivation		
High-degree T-EPVS	2.065 (1.277-3.339)	**0.003**
High-degree CS-EPVS	1.219 (0.676-2.199)	0.509
High-degree BG-EPVS	0.933 (0.568-1.533)	0.784
Affective dysregulation		
High-degree T-EPVS	2.444 (1.576-3.791)	**<0.001**
High-degree CS-EPVS	1.270 (0.756-2.134)	0.366
High-degree BG-EPVS	1.181 (0.752-1.855)	0.470
Impulse dyscontrol		
High-degree T-EPVS	3.266 (1.841-5.794)	**<0.001**
High-degree CS-EPVS	0.863 (0.442-1.685)	0.666
High-degree BG-EPVS	0.615 (0.345-1.096)	0.099
Social inappropriateness		
High-degree T-EPVS	2.601 (0.943-7.173)	0.065
High-degree CS-EPVS	0.815 (0.249-2.67)	0.736
High-degree BG-EPVS	3.060 (0.916-10.217)	0.069
Abnormal perception		
High-degree T-EPVS	3.763 (1.526-9.281)	**0.004**
High-degree CS-EPVS	1.235 (0.37-4.118)	0.731
High-degree BG-EPVS	0.620 (0.262-1.467)	0.277

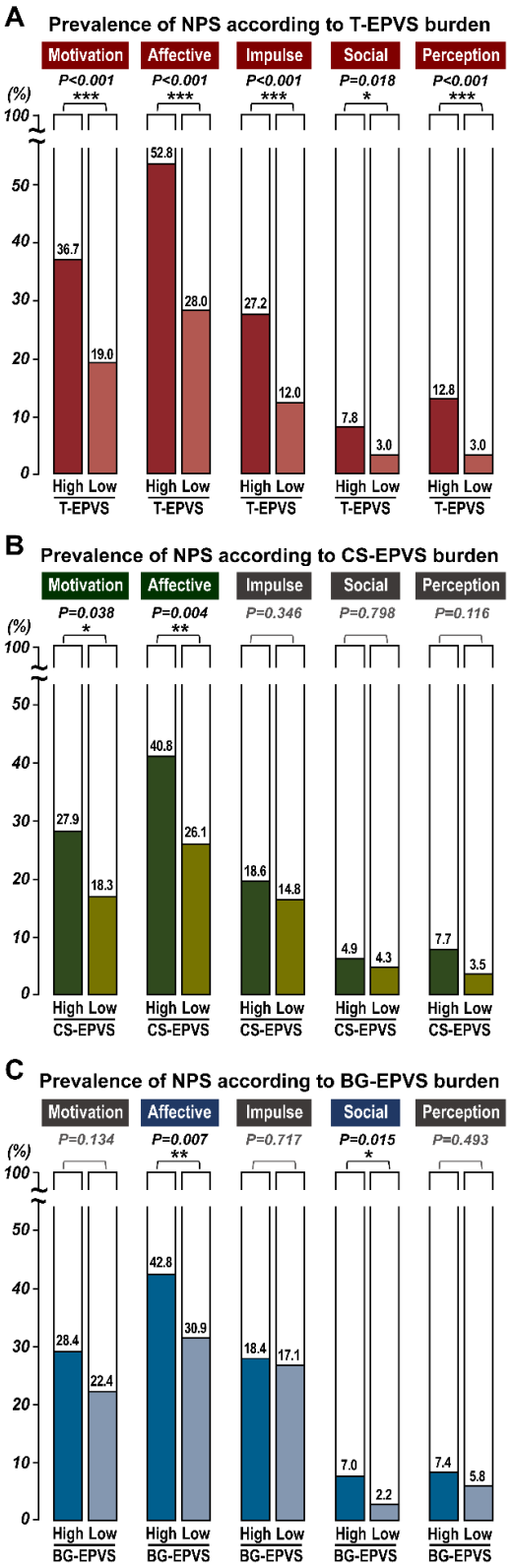

Figure 4. Prevalence of NPS according to regional EPVS burden. In each behavioral domain (decreased motivation, affective dysregulation, impulse dyscontrol, social anappropriateness, and abnormal perception), the frequency of NPS is compared between high-degree and low-degree group in T-EPVS, CS-EPVS, and BG-EPVS.

IV. DISCUSSION

Our findings provide four major findings: (1) Frequency of high-degree BG-EPVS and T-EPVS increases according to severity of cognitive symptoms (i.e., in the order of SCI, MCI, and dementia), indicating that EPVS burden tend to reveal an increasing trend towards worsening of cognitive dysfunction. (2) While BG-EPVS were significantly associated with systemic vascular risk factors and higher burden of other SVD imaging biomarkers, T-EPVS did not reveal any association with conventional vascular risk factors or SVD markers, shedding light that T-EPVS may be rather suggestive of non-vascular etiologies. (3) BG-EPVS appears to have an independent association with cognition in drug-naïve PD even after adjusting for DAT availability and other SVD markers. Although the effects were partially mediated by other SVD markers (WMH for language domain and visual memory domain), high-degree BG-EPVS still exerted direct effect on cognitive performance. (4) PD patients with high-degree T-EPVS were likely to exhibit higher burden of neuropsychiatric symptoms and the association appears to be independent with other SVD markers or nigrostriatal denervation. Collectively, these findings suggest that impaired perivascular clearance may contribute to cognitive and neuropsychiatric symptoms in PD and that each symptom may be associated with increased EPVS burden in distinct anatomical regions (i.e., T-EPVS for neuropsychiatric symptom, BG-EPVS for cognition).

The underlying pathology for regional EPVS in PD is poorly understood. Higher burden of CS-EPVS and BG-EPVS were likely to be associated with older age and higher frequencies of systemic vascular comorbidities. Moreover, high-degree BG-EPVS was associated with other cerebral SVD imaging markers (higher burden of deep/periventricular WMH and presence of lacune or lobar/deep CMBs). These findings support that BG-EPVS/CS-EPVS may have presumed vascular etiologies. Meanwhile, high-degree T-EPVS was only associated with older age without revealing any significant association with systemic vascular risk factors or other imaging markers for SVD. However,

the authors are reluctant to conclude that increased T-EPVS burden is merely suggestive of normal aging process considering its significant association with neuropsychiatric symptom burden and PDD observed in this present study. Apart from vascular etiologies, dysfunctional clearance of pathological protein constitutes one of the major pathophysiology underlying EPVS in that abnormal protein aggregation is known to clog up the PVS surrounding the cortical arteries upstream, inducing stagnation of interstitial fluid flow and retrograde dilation of PVS.[3]

Although cognitive implications of EPVS burden in neurodegenerative disorders have been highly inconsistent across studies[15-17], significant association between high-degree BG-EPVS and worse cognition have been consistently observed in PD population.[9, 27, 28] In line with previous studies, patients with high-degree BG-EPVS exhibited worse performance in language, visual memory, and frontal/executive domain in this present study (Model 1). However, recent studies have raised concern whether BG-EPVS directly affect cognitive dysfunction or their association is mediated by other concomitant pathologies.[15-17, 28] For example, a recent study reported that high-degree BG-EPVS is only indirectly associated with cognitive dysfunction through other SVD markers such as lacunar infarcts or WMH rather than exhibiting direct contribution.[15] Similarly, the association between high-degree BG-EPVS and worse frontal/executive dysfunction was no longer significant when further adjusting for SVD markers (deep/periventricular WMH burden and presence of lacune, Model 2). In secondary analyses seeking for factors that mediate the association between BG-EPVS and cognition, frontal/executive dysfunction was fully mediated by WMH burden (Figure 3C), suggesting that the effect of BG-EPVS on frontal/executive function may be attributable to other closely linked SVD markers that disrupt the frontal-subcortical circuit rather than BG-EPVS itself.[15] Meanwhile, high-degree EPVS were associated with poor language and visual memory domain even after adjusting for SVD markers along with clinical factors and DAT availability (Model 2). Path analysis confirmed that high BG-EPVS burden exerted direct effect on language and memory dysfunction although the effect was partially mediated by WMH burden (Figure 3A and 3B), implying that BG-EPVS itself may indeed play an independent role in cognitive dysfunction. However, we cannot exclude the possibility that there may be another unknown factor that may mediate the effect of BG-EPVS towards this relationship. Of note, a recent study reported that BG-EPVS has direct effect on cognitive outcomes in

PD, while the association is partially mediated by cerebrospinal fluid biomarkers (amyloid-β and tau).[28] Future studies incorporating multiple biomarkers (e.g., alpha-synuclein, amyloid, and tau) along with SVD markers are required for further elucidation.

Besides BG-EPVS, EPVS burden in the other two locations did not reveal any significant association with cognitive performance in each domain. Although high-degree T-EPVS group showed greater frontal/executive dysfunction compared to low-degree T-EPVS group even after adjusting for other SVD markers (P=0.039), the difference was no longer significant after controlling for multiple comparison correction. Even though T-EPVS severity did not reveal significant difference in domain-specific cognitive performance, it is noteworthy that an increasing trend towards high frequency of high-degree T-EPVS with regards to worsening cognitive status was observed in our study. This discrepancy may have stemmed from our cross-sectional study design. Considering that the temporal relationship between development of EPVS and cognitive symptoms remains elusive, cross-sectional association may be insufficient to reflect to cognitive implication of T-EPVS. In line with our speculation, previous study have reported that EPVS may be predictive of future cognitive decline while the associated was not significant cross-sectionally.[28] Alternatively, this may be explained by greater NPS burden in high-degree T-EPVS, given that incidence and burden of NPS tend to be coupled with cognitive impairment serving as a major risk factor for PDD conversion.[29-31]

Along with cognition, NPS have a significant impact on function, quality of life, and caregiver burden in PD and holds prognostic value leading to faster functional impairment and progression to death.[32] Despite recent growing interest in EPVS in PD, the relationship between NPS and regional EPVS are poorly understood. Our findings demonstrates that increased burden of T-EPVS may be associated with higher burden of NPS in decreased motivation, affective dysregulation, and impulse dyscontrol and abnormal perception domains even after adjusting for clinical factors, DAT availability and other SVD markers (Table 3). Although our data is insufficient to uncover the mechanism underlying the association between T-EPVS and higher burden of neuropsychiatric symptoms, we offer several plausible explanations for this finding. First, high T-EPVS burden may have served as microvascular lesions directly affecting the circuits taking part in the development of NPS, a phenomenon represented by “vascular depression hypothesis” or “vascular apathy hypothesis”.[33-36] According to the hypotheses, cerebral SVD contribute to neuropsychiatric

symptom either by directly involving the white matter networks (e.g., frontal-subcortical or fronto-limbic circuits) or by damaging gray matter indirectly via reduced cerebral blood flow or compromising the blood-brain barrier.[34] Although earlier studies mainly focused on lesions that actually disrupt the white matter (e.g., WMH or lacune)[34], several lines of evidence suggests that even microvascular lesions such as EPVS could also critically affect the circuits associated with mood regulation by directly compressing or disrupting the white matter tracts.[35, 36] Second, increased NPS burden may be attributable to other non-vascular pathologies associated with high-degree T-EPVS. Given the significant association between T-EPVS and cerebral amyloidosis observed in a recent study[14], amyloid deposition may serve as one of the potential candidates mediating this association. It is well-known that presence of amyloid pathology is associated with greater incidence and burden of NPS in aging and various neurodegenerative disorders.[37-40] Moreover, coexistent AD pathology is known to harbor greater NPS burden in Lewy body disease.[37, 38] Future studies investigating the association between NPS, T-EPVS and amyloid pathology in PD population should be followed to confirm this speculation.

Our study had several limitations. First, the estimation of EPVS burden was based on visual rating which may not be sensitive enough to reflect the true EPVS burden, thereby preventing us from performing quantitative analyses. Although visual rating system for EPVS is widely used and holds acceptable inter-rater variability, visually rated EPVS burden is inevitably vulnerable to proficiency of raters. Second, considering the inherent limitation of retrospective, cross-sectional study design, no causal relationship between regional EPVS burden and clinical measures could be drawn from this study. More importantly, it was impossible to explore whether regional EPVS hold prognostic value in PD. Third, our study lacks histopathological confirmation or supporting biomarkers, which prevents us from understanding the true pathophysiology underlying EPVS in each region.

Nevertheless, our study holds several strengths over previous studies. First, assessment of NPS and cognition was conducted prior to initiation of anti-parkinsonian therapy in this study. Considering that NPS in patients is highly influenced by dopaminergic replacement therapy, our study population may be optimal to decipher the potential association between NPS and EPVS burden. Second, our study includes large population of well-characterized de novo PD who underwent 18F-FP-CIT PET scan, MRI, neuropsychological and neuropsychiatric assessment at baseline, thereby allowing us to explore the differential role

of region-specific EPVS burden throughout the cognitive and neuropsychiatric spectrum of PD. Lastly, to our knowledge, this is the first report that investigate the prevalence and clinical implication of T-EPVS in PD population.

V. CONCLUSION

In conclusion, BG-EPVS and T-EPVS appears to exert differential effects on cognition and neuropsychiatric symptoms in patients with PD. Investigating the EPVS profile in distinct anatomical regions may serve as useful imaging biomarkers for disentangling the heterogeneity of PD.

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ABSTRACT(IN KOREAN)

파킨슨병에서의 인지 기능 및 신경정신과적 증상에 대한 확장성 혈관주변공간 위치의 다변적 의미

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배경: 파킨슨병에서 확장성 혈관주변공간(EPVS)의 잠재적인 역할을 밝히는 연구가 늘고 있지만, 위치에 따른 EPVS와 인지 기능 및 신경정신 증상과의 관계는 여전히 논의의 여지가 있습니다. 본 연구에서는 상대적으로 큰 규모의 아직 치료를 받지 않은 파킨슨병 환자 집단에서 위치에 따른 EPVS 및 이와 인지 기능 및 신경정신 증상과의 연관성을 조사하였습니다.

방법: 초기 평가 단계에서 자기 공명 영상 (MRI), 도파민 수송체(DAT) 스캔, 신경심리학적 검사 및 신경정신 증상에 대한 평가를 받은 480명의 파킨슨병 환자(인지적으로 영향을 받지 않은 환자 123명, 경도 인지 장애 291명, 치매 66명)에서 위치에 따른 EPVS를 직접 세어 평가하였습니다. T-EPVS 및 BG-EPVS는 어느 반구에서든 10개를 초과할 때 "높은 정도"로 정의하였으며, CS-EPVS의 경우 20개가 기준이었습니다. 위치에 따른 EPVS 정도에 따라 인지 기능 및 신경정신 증상과 혈관 위험 요인, 소혈관 질환 (SVD) 영상 표지자 및 DAT 가용성을 비교하였습니다.

결과: 높은 정도의 T-EPVS (P <0.001) 및 BG-EPVS (P = 0.001) 비율은 인지 범위 악화 순서로 증가하는 추세를 보였습니다. 높은 정도의 BG-EPVS 그룹은 혈관 동반 질환 (고혈압 및 심장 질환) 비중이 높고, 인지 성능 (언어 및 시각 기억 영역), SVD 부담이 낮았습니다. 높은 정도의 T-EPVS 그룹은 동기부여 감소 (P = 0.004), 감정 조절 이상 (P <0.001) 및 충동 통제 이상 (P <0.001) 측면에서 높은 신경정신 부담 경향을 보였습니다. 한편, CS-EPVS의 부담이 높아지면 더 나이가 들고 고혈압이 동반되었으며, 인지나 신경정신 증상에는 차이가

없었습니다.
결론: BG-EPVS와 T-EPVS는 PD 환자의 인지 및 신경정신 증상에 각기 다른 영향을 미치는 것으로 보입니다. 다양한 위치에서의 EPVS는 파킨슨병의 다변적 임상적 특성을 보여주는 유용한 이미징 바이오마커로 작용할 수 있습니다.

핵심되는 말 : 파킨슨병, 글림프 시스템, 인지장애, 무감동, 정서적 기분 장애