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Perivascular Space in Parkinson's disease: Association with CSF Amyloid/Tau and Cognitive decline

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Abstract

Objective: Whether perivascular space (PVS) visible on magnetic resonance imaging (MRI) represents glymphatic dysfunction and whether this imaging marker is pathologic in Parkinson's disease (PD) have been controversial. The objective was to determine whether PVS visible on MRI is independently associated with cognitive decline in patients with PD, and to test whether pathologic proteins in the CSF (such as $A\beta_{42}$) mediate the pathologic role of PVS.

Methods: A total of 341 patients with Parkinson's disease from Parkinson's Progression Marker Initiative (PPMI) cohort was included in the present study. PVS in the basal ganglia (BG-PVS) and centrum semiovale were evaluated with a semiquantitative scale. Changes in the Montreal Cognitive Assessment (MoCA) score and the absolute MoCA score at the 3-year assessment were considered the main cognitive outcome. A multivariable linear regression model was used to test the association between PVS and cognitive decline. A mixed linear model and path analysis were used to test the interaction among PVS, CSF biomarkers and cognitive decline.

Results: BG-PVS was associated with cognitive decline in patients with PD at the 3-year follow-up independent of age, baseline cognition, motor and nonmotor function, presynaptic dopaminergic deficiency, and CSF biomarkers. The interaction between BG-PVS and $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, and $A\beta_{42}$ levels was significantly predictive of 3-year cognitive decline. Path analysis confirmed that CSF $A\beta_{42}$/tTau levels partially mediated the pathologic effect of BG-PVS on cognitive outcome in PD.

Conclusions: BG-PVS is independently associated with cognitive decline in PD, and this association may be partially mediated by toxic CSF proteins.

Keywords: Parkinson's disease; Perivascular Space; Cognition; Amyloid; Tau

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with α-synuclein (α-syn) aggregation and Lewy body deposition being the pathologic hallmarks. Previous studies from several cohorts consistently reported that Alzheimer's disease (AD)-related CSF biomarkers (i.e., lower levels of $A\beta_{42}$ and $A\beta_{42}$/Tau ratios and higher levels of total and phosphorylated Tau) were associated with cognitive impairment in PD cross-sectionally[1-3] and longitudinally [4-6].

Emerging evidence has highlighted the role of the perivascular space (PVS) as a glymphatic pathway for waste clearance in the brain and demonstrated that glymphatic dysfunction reduced cerebrospinal fluid (CSF) clearance of Aβ in AD models and in patients with AD [7-9]. Since AD-related proteins are toxic to neurons and glial cells[10] and are associated with cognitive decline in AD and PD, it is possible that reduced CSF clearance of toxic proteins as a result of glymphatic dysfunction may aggregate the neurodegenerative process and facilitate the development of dementia. A previous cohort from Korea demonstrated that basal-ganglia PVS (BG-PVS) visible on MRI predicted cognitive decline in PD at the 5-year follow-up [11]. This result needs to be validated in other cohorts. In addition, if BG-PVS visible on MRI reflects glymphatic dysfunction, there might be an association between the severity of BG-PVS visible on MRI and higher neurodegenerative burden measured by CSF biomarkers such as Aβ.

The Parkinson's Progression Marker Initiative (PPMI) is the largest ongoing cohort of PD with comprehensive clinical, imaging and CSF biomarker data. The PPMI provides an opportunity to confirm the pathologic role of BG-PVS in PD cognitive outcome. In addition, it provides superb data to test the relationship between PVS visible on MRI and neurodegenerative burden measured by CSF biomarkers, which may inform the mechanism and potential therapeutic target of PVS in progressive neurodegenerative processes.

2. Method

2.1 Study design and participants

PPMI is an ongoing, multicenter, longitudinal, observational study that started in 2010 (https://www.ppmi-info.org/). Patients with early, drug-naïve PD and intact cognition were included. The PPMI study was approved by the institutional review board at each site, and participants provided written informed consent to participate. The protocol and more detailed study design of PPMI has been described elsewhere [12]. From the whole PPMI cohort, only PD patients with complete baseline BG-PVS profiles and CSF biomarkers were included in the present analysis. The data used in the current study were downloaded from the PPMI dataset in June 2020.

2.2 Outcome measurements

Cognitive decline was evaluated using the change in the MoCA score from baseline to 3-year follow-up and the absolute MoCA score at the 3-year assessment. The Hopkins Verbal Learning Test (HVLT) (memory), the Benton Judgment of Line Orientation 15-item version (visuospatial function), the Symbol-Digit Modalities Test (processing speed), the Letter Number Sequencing (executive function and working memory), and the semantic (animal) fluency test (language) were also performed. Motor function was measured using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III and Hoehn-Yahr stage. Nonmotor symptoms in the prediction of cognitive decline in PD included rapid eye movement behavior disorder (RBD), which was assessed with the RBD Screening Questionnaire (RBDSQ); sense of smell, which was assessed with the University of Pennsylvania Smell Identification Test (UPSIT); depression, which was assessed with the

15-item Geriatric Depression Scale (GDS); and anxiety, which was assessed with the State-Trait Anxiety Inventory.

2.3 DAT imaging

[123I]β-CIT DAT single-photon emission computed tomography (SPECT) imaging was acquired at PPMI imaging centers in accordance with the PPMI imaging protocol. Mean caudate and putaminal uptake relative to uptake in the occipital area and asymmetry of caudate and putaminal uptake (side with highest divided by side with lowest uptake) were computed for the analysis.

2.4 History of cardio- and cerebrovascular diseases and risk factors

Histories of cardio- and cerebrovascular diseases were recorded in the PPMI cohort at patient screening. Cardiovascular diseases and risk factors include a history of diabetes, hypertension, hyperlipidemia, hypercholesterolemia, and cardiac diseases. Cerebrovascular diseases included a history of cerebrovascular accident, transient ischemic attack, ischemic stroke, cervical and carotid stenosis or occlusion.

2.5 Imaging markers of cerebral small vessel disease

Imaging markers of cerebral small vessel disease (CSVD) were evaluated by a neurologist who was blind to the patient information (HJ Wan) following the instruction and definition of STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) [13]. White matter hyperintensity (WMH) was rated according to the Fazekas rating scale [14]. Perivascular space was defined on MRI as small, sharply delineated structures of CSF intensity (or close to CSF intensity) following the course of perforating vessels. PVS in the basal ganglia and centrum semiovale (CS-PVS) were rated separately on T2 weighted sequence as 0 = none, 1 = 1–10, 2 = 11–20, 3 = 21–40, and 4 = >40 PVS per side, and the worse side was used if there was asymmetry [15, 16]. In the statistical analysis for BG-PVS, patients were stratified into groups with moderate-to-severe BG-PVS (BG-PVS rating≥2) and none-to-mild BG-PVS (BG-PVS rating<2). Similarly, in the analysis for WMH and CS-PVS, patients were also grouped into the high WMH group (Fazekas>2) versus the low WMH group (Fazekas≤2) and the high CS-PVS group (CS-PVS rating≥2) versus the low CS-PVS group (CS-PVS rating<2). This stratification was consistent with the distribution of CSVD profiles in our data and was consistent with studies showing that BG-PVS rating≥2 (moderate to severe) was predictive of unfavorable outcomes [15, 16].

2.6 Genotyping

At the screening visit, genomic DNA was extracted from whole blood of the subject. The APOE genotype was analyzed at the PPMI genetic core as previously described [17]. Subjects were classified by the presence or absence of *APOE* ε4 genotypes.

2.7 CSF biomarkers

The concentration of α-synuclein in CSF samples was analyzed using an ELISA assay available commercially from BioLegend. CSF $A\beta_{42}$, total tau (tTau) and tau phosphorylated at the threonine 181 position (pTau) were analyzed at Biorepository Core laboratories to the University of Pennsylvania using Elecsys electrochemiluminescence immunoassays (Roche Diagnostics). More detail and primary results of the measured CSF biomarkers have been reported previously in the PPMI cohort [17, 18].

2.8 Statistics

Continuous variables were compared between groups using the Mann-Whitney test (nonnormal distribution) or two sample t test (normal distribution), and categorical variables were compared between groups using the Chi-square test. Univariate and multivariable linear regression models were performed using the MoCA score at the 3-year follow-up and the 3-year change in the MoCA score as separate dependent variables. The regression models consulted a previous PPMI study using 2-year cognitive outcomes [19]. Variables showing a tendency to significant association ($p<0.1$) further entered the multivariable linear regression analysis simultaneously, while only one significant variable of the same feature with lower P value was selected to avoid collinearity. As CSF biomarkers were significantly correlated with each other (supplementary figure 1)[20], each biomarker entered the multivariable regression model separately.

The interaction between BG-PVS and CSF biomarkers in relation to cognition was first explored by plotting the fitting curve and then by linear mixed models. The change in MoCA score and MoCA score at the 3-year follow-up was used as dependent variables in linear mixed models, BG-PVS severity and CSF biomarker with or without interaction term were set as fixed effects, and other variables showing significant association with cognitive outcomes in multivariable regression were used as random effects. The Akaike information criterion (AIC) of models with and without the BG-PVS*CSF biomarker interaction item was recorded. Path analysis was conducted to investigate how much CSF biomarkers mediated the effect of BG-PVS on cognition in PD. The standardized coefficient (β) of BG-PVS without a mediation effect (direct effect) and with a mediation effect (indirect effect) and the standardized coefficient (β) of the CSF biomarker on the change in MoCA were calculated. P value < 0.05 was defined as significant. Group comparison of CSF biomarkers at each follow-up point was also performed between PD groups with different BG-PVS severities. P value < 0.01 was defined as significant in this group comparison for multiple comparison correction (Bonferroni correction for 4 repeated comparisons). Group comparison was conducted in SPSS 25.0 (SPSS, inc., Beijing, China), and linear regression and linear mixed models were performed in R software version 4.02

(https://www.r-project.org/).

To rule out confounding by other CSVD markers and to investigate the location specificity of PVS, the relationship among WMH or CS-PVS, CSF biomarkers, and cognitive decline was further explored using a similar statistical approach.

2.9 Data Availability Statement.

The data was publicly available on PPMI website (https://www.ppmi-info.org/access-data-specimens/).

3. Results

3.1 Baseline features of the included patients

Four hundred and twenty three patients with drug-naïve PD were recruited in PPMI cohort. Among these subjects, MRI imaging or T2-weighted imaging was missing in 47 patients, and imaging in another 13 patients was not qualified to rate BG-PVS due to incomplete or nonaxial slices. CSF biomarkers were missing in another 22 patients with PD. Finally, 341 patients with complete baseline PVS and CSF biomarkers were included in the present analysis. The included and excluded patients showed overall similar demographic and behavioral profiles (supplementary table 1).

3.2 Group comparison between patients with lower and higher BG-PVS burdens

Compared with patients with lower BG-PVS burden, patients with more severe BG-PVS were significantly older; had more impaired motor function at baseline; had a higher prevalence of previous cardiovascular disease and more severe WMH at baseline; had a higher risk of cognitive impairment and a greater decline in the MoCA score at the 3-year follow-up despite of similar baseline MoCA scores; and showed lower levels of CSF α-synuclein, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau and higher levels of CSF tTau and pTau at baseline (**Table 1**).

3.3 Univariate linear regression for cognition at the 3-year follow-up

Using the absolute MoCA score at the 3-year follow-up as the dependent variable, age, baseline MoCA score, MDS-UPDRS III score, RBDSQ, UPSIT score, CSF $A\beta_{42}$, tTau, pTau, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, putamen asymmetry and BG-PVS were significantly associated with cognition at the 3-year follow-up in PD patients ($P<0.05$).

Using decline in MoCA score as the dependent variable, age, baseline MoCA score, RBDSQ, UPSIT score, CSF $A\beta_{42}$, tTau, pTau, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, putamen asymmetry and BG-PVS were significantly associated with cognitive decline during three years in PD patients ($P<0.05$) (supplementary table 2).

3.4 *Multivariable linear regression for cognition at the 3-year follow-up*

In multivariable regression models, BG-PVS was significantly associated with MoCA score or change in MoCA score, independent of age, baseline cognition, motor function, nonmotor symptoms, presynaptic dopaminergic deficiency, and CSF biomarkers. Baseline CSF $A\beta_{42}$, $A\beta_{42}$/tTau and $A\beta_{42}$/pTau were significantly associated with the MoCA score or change in the MoCA score at 3-year follow-up independent of age, baseline cognition, motor function, nonmotor symptoms, presynaptic dopaminergic deficiency, and BG-PVS. However, baseline CSF tTau and pTau were not significantly associated with either cognitive outcome at year three after adjustment (supplementary table 3).

3.5 *Interaction between CSF biomarkers and BG-PVS*

There was a significant main effect of BG-PVS and CSF $A\beta_{42}$/tTau, $A\beta_{42}$/pTau and $A\beta_{42}$ as well as interactions between BG-PVS and these CSF biomarkers (**Table 2**), such that patients with higher BG-PVS and lower $A\beta_{42}$/tTau (**Figure 1A**), $A\beta_{42}$/pTau (**Figure 1B**), or $A\beta_{42}$ (**Figure 1C**) showed steeper decline in the MoCA score at the 3-year follow-up. Models containing interaction terms provided a slightly improved fit. As patients with a higher BG-PVS burden had a higher prevalence of cardiovascular disease and risk factors, we further tested whether the interaction between BG-PVS and CSF biomarkers was confounded by the presence of cardiovascular disease and risk factors. However, the correlation between CSF biomarkers and cognitive decline was not stratified by the presence of cardiovascular disease or related risk factors (supplementary figure 2).

We further compared CSF biomarkers at each follow-up timepoint between the BG-PVS groups. The results revealed that patients with more severe BG-PVS showed significantly higher levels of all measured CSF biomarkers at baseline, 1-year follow-up, and 2-year follow-up, and the significant difference in tTau and pTau was still observed at year three (supplementary table 4) with corrected P values ($P<0.01$).

3.6 ***Path analysis***

In path analysis, CSF $A\beta_{42}$/tTau was found to mediate the effect of BG-PVS on cognitive decline (total effect [original coefficient] = -0.256, direct effect [corrected coefficient] = -0.208, indirect effect = -0.048) (**Figure 2A**). That is, CSF $A\beta_{42}$/tTau mediated 18.8% (indirect effect/total effect) of the BG-PVS effect on the decrease in MoCA scores during the 3-year follow-up. In path analysis, the correlation of BG-PVS with $A\beta_{42}$/pTau was marginally significant, and that with $A\beta_{42}$ was not significant (**Figure 2B and 2C**).

3.7 ***Additional analysis with WMH and CS-PVS***

For WMH, no significant difference in baseline CSF biomarkers (α-syn z = -1.337, P = 0.181; $A\beta_{42}$ z = -0.430, P = 0.667; pTau z = -1.181, P = 0.238; tTau z = -1.697, P = 0.090) was found between groups with different WMH severity (Fazekas 0-2 vs. Fazekas 3-6). No significant correlation was found between CSF biomarkers and WMH Fazekas rating according to the Spearman correlation analysis (α-syn r = 0.025, P = 0.640; Aβ_{42} r = -0.057, P = 0.300; pTau r = 0.036, P = 0.534； tTau r = 0.039, P = 0.331). No significant correlation was observed between WMH and cognitive decline or between WMH and CSF biomarkers (Aβ_{42}/tTau, Aβ_{42}/pTau, Aβ_{42}) in the path analysis (supplementary figure 3).

For CS-PVS, no significant difference in baseline CSF biomarkers (α-syn z = -1.391, P = 0.164; Aβ_{42} z = -0.685, P = 0.493; pTau z = -1.422, P = 0.155； tTau z = -1.741, P = 0.082) was found between groups stratified by CS-PVS severity (CS-PVS 0-1 vs. CS-PVS≥2). No significant correlation was observed between CS-PVS and CSF biomarkers (Aβ_{42}/tTau, Aβ_{42}/pTau, Aβ_{42}) in path analysis (supplementary figure 3). Although a marginally significant correlation between CS-PVS and cognitive decline was observed in the path analysis, the significant correlation was not preserved in the multivariable linear model adjusting for age (coefficient = -0.729, 95% CI = -1.612–0.154, P = 0.105) or in the model adjusted for age, baseline MoCA scores, baseline state trait anxiety score, RBDSQ, UPSIT, and putamen asymmetry (coefficient = -0.615, 95% CI = -1.419–0.188, P = 0.132).

4. Discussion

This is the first study that examined the relationship between CSF biomarkers and PVS visible on MRI in neurodegenerative disease. The main finding demonstrated that BG-PVS was independently associated with cognitive decline in patients with PD. In addition, BG-PVS modified the pathologic effect of Aβ_{42}/tTau, Aβ_{42}/pTau, and Aβ_{42} on cognitive decline in PD. Path analysis confirmed that CSF biomarkers, especially Aβ_{42}/tTau, partially mediated the pathologic effect of BG-PVS on cognitive outcomes in PD. These results suggest that the increased visibility of BG-PVS on MRI may reflect more advanced glymphatic dysfunction, resulting in higher levels of toxic CSF proteins, which may in turn accelerate neurodegenerative processes and cognitive decline. It also implies that the glymphatic pathway may serve as a therapeutic target to preserve cognition in neurodegenerative disease.

Our results validated a previous study by Park and colleagues and showed that BG-PVS was associated with 3-year cognitive decline in patients with PD[11]. In addition, the contribution to poor cognitive outcome and the interaction with CSF proteins were specific for PVS located in the basal ganglia but not the centrum semiovale. However, the underlying mechanism for the location specificity remains unclear. Evidence suggests that cerebral arterial pulsation drove CSF-interstitial fluid exchange mediated by the glymphatic pathway [21], and arterial stiffness was associated with a higher BG-PVS burden [22]. It is possible that PVS in the basal ganglia may be more prone to arterial damage and pulsation change during aging. However, we did not test arterial function, such as arterial stiffness and regulation. Future studies will be needed to test this hypothesis. In addition, BG-PVS differs from CS-PVS in structure, as BG-PVS is covered by two leptomeningeal membranes and directly connects CSF [23]. This means that BG-PVS may be more active in eliminating waste from CSF, and the increased visibility of BG-PVS may represent an increased effort in waste clearance. Future studies directly comparing CSF dynamics are needed to investigate the location difference of PVS.

Moreover, the results also suggested that PVS visible on MRI may reflect glymphatic dysfunction and impaired efflux of CSF proteins in patients with PD. In addition, the level of neurodegenerative CSF proteins ($A\beta_{42}$/tTau) partially mediated the effect of BG-PVS on poor cognitive outcome. Taking that CSF proteins, including Aβ and Tau, are toxic to neurons and glial cells [10] and AD biomarkers are predictive of cognitive decline in PD [4-6], the result implies that BG-PVS may contribute to cognitive decline by elevating toxic CSF proteins in patients with PD. The glymphatic pathway has drawn much attention in recent years as a novel pathway to exclude neurotoxic proteins and a potential therapeutic target [24]. In patients with superficial sclerosis, PVS was enlarged beneath the affected area where Aβ was deposited in the cortical arterial wall by biopsy, supporting the notion that enlarged PVS is a sign of a blocked drainage pathway by proteins such as Aβ [25]. Therefore, PVS visible on MRI may be a possible way to explore the static glymphatic pathway offline.

The interactive effect between BG-PVS and CSF $A\beta_{42}$, $A\beta_{42}$/tTau, and $A\beta_{42}$/pTau on cognitive decline was a novel finding in our study. This suggests that modification of the glymphatic pathway may be a potential and crucial therapeutic target to alleviate the pathologic effect of $A\beta_{42}$ and Tau on cognitive decline in PD. Emerging evidence has demonstrated the interaction between PVS and AD-related proteins [24], and our result further supported the additive consequence of their interaction in human cohort. In addition, the benefit of treatment targeting the glymphatic pathway may be beyond AD-related pathology since PVS has also been highlighted to be involved in the inflammatory process in multiple sclerosis [26] Sleep intervention may be an effective way to improve glymphatic function, which may need to be tested in clinical trials or observational studies [27]. Other treatments targeting pericytes, endothelial cells, perivascular inflammation and other factors pertaining to glymphatic function also deserve to be investigated.

In addition to our initial hypothesis, the factors associated with 3-year cognitive decline were largely consistent with previous 2-year follow-up analysis [19]. More recently, Irwin and colleagues reported that AD-related CSF biomarkers were associated with 3-year cognitive decline in a PPMI cohort [20]. Although finding risk factors associated with cognitive decline was not the main topic of our study, the consistency with previous data suggests that the present data are representative of the whole cohort despite missing BG-PVS data in 59 patients (missing rate = 13.9%).

We acknowledge several limitations. First, this study did not measure the dynamic function of the glymphatic pathway in vivo. Currently, dynamic fluid exchange by the glymphatic pathway has been investigated in vivo by intrathecal injection of the contrast agent in neurological diseases such as idiopathic normal pressure hydrocephalus [9, 28]. These approaches enable tracking uptake and distribution of tracers dynamically, but they are invasive and may not be applicable in patients with PD. Second, although CSF $A\beta_{42}$ and Tau are consistently found to be associated with cognitive decline in PD, they are not PD-specific biomarkers. In addition, the findings of the present study only represent the PD population. Whether proteinaceous waste such as Aβ and Tau drives the increased visibility of PVS on MRI and potentially mediates its toxicity needs to be tested in the AD population and normal aging population.

In conclusion, we found that BG-PVS may be independently associated with cognitive decline in PD, which may be partially mediated by toxic CSF proteins. The increased visibility of BG-PVS on MRI may reflect more advanced glymphatic dysfunction. PVS may serve as a therapeutic target to preserve cognition in PD.

Conflict of interest

None

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Figure legends

Figure 1. Correlation between CSF biomarkers and cognitive outcomes stratified by BG-PVS

BG-PVS modified the effect of $A\beta_{42}$/tTau (A), $A\beta_{42}$/pTau (B), $A\beta_{42}$ (C) on cognitive outcome in Parkinson's disease, as high BG-PVS group showed steeper decline in the MoCA score in relation to CSF biomarkers at the 3-year follow-up.

Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid.

Figure 2. Path analysis

A. CSF $A\beta_{42}$/tTau, but not $A\beta_{42}$/pTau or CSF $A\beta_{42}$ significantly mediated the effect of BG-PVS on cognitive decline in patients with PD. The effect of WMH (B) or CS-PVS (C) on cognitive outcome was not mediated by CSF biomarkers.

Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid; WMH, white matter hyperintensity.

Supplementary figures:

FIG. S1. Correlation between CSF biomarkers

Abbreviations: CSF, cerebrospinal fluid.

FIG. S2. Correlation between CSF biomarkers and cognitive decline stratified by the presence of cardiovascular disease

The presence of cardiovascular disease did not modify the effect of CSF biomarkers on cognitive decline in patients with PD.

FIG. S3. Path analysis for WMH, CS-PVS and CSF biomarkers

CSF biomarkers did not mediate the effect of WMH or CS-PVS on cognitive decline in PD.

Table 1. Demographic information between groups stratified by BG-PVS

	PD with low BG-PVS (N = 286)	PD with high BG-PVS (N = 55)	P value
Demographic			
Age (median, IQR, year)	60.7 (53.5–66.6)	71.1 (67.1–74.8)	**<0.001**
Gender (F/M)	100/188	15/40	0.269
Disease profile			
Disease duration (median, IQR, month)	4 (2–7)	6 (3–13)	0.066
MoCA Score (median, IQR)	28 (26–29)	27 (25–29)	0.222
Hoehn-Yahr staging (median, IQR)	2 (1–2)	2 (2–2)	**0.001**
MDS-UPDRS III total (median, IQR)	19 (14–26)	22 (16–27)	**0.024**
State Trait Anxiety Score (median, IQR)	94 (89–98)	94 (88–97)	0.500
Geriatric Depression Scale (median, IQR)	5 (5–6)	5 (4–6)	0.280
CSF biomarkers			
CSF α-synuclein (median, IQR, pg/ml)	1351.3 (1029.3–1718.0)	1528.8 (1164.3–2086.0)	**0.016**
CSF $A\beta_{42}$ (median, IQR, pg/mL)	848.6 (615.1–1119.0)	822.2 (627.9–1050.5)	0.860
CSF pTau (median, IQR, pg/mL)	13.0 (10.9–16.7)	15.4 (12.4–21.4)	**0.001**
CSF tTau (median, IQR, pg/mL)	152.6 (124.0–192.6)	186.4 (147.2–237.7)	**<0.001**
CSF $A\beta_{42}$/tTau	5.81 (4.69–6.69)	4.88 (3.71–6.01)	**0.002**

CSF $A\beta_{42}$/pTau	69.4 (57.4–80.3)	61.1 (42.7–75.7)	**0.002**
DAT striatal binding ratios			
Mean caudate uptake (median, IQR)	2.02 (1.67–2.37)	1.88 (1.54–2.21)	0.155
Mean putamen uptake (median, IQR)	1.79 (1.48–2.18)	1.77 (1.34–2.08)	0.270
Caudate asymmetry (median, IQR)	1.19 (1.10–1.31)	1.17 (1.07–1.27)	0.216
Putamen asymmetry (median, IQR)	1.45 (1.19–1.76)	1.39 (1.17–1.73)	0.484
Small vessel disease profile			
WMH Fazekas score (median, IQR)	2 (1–2)	3 (2–4)	**<0.001**
Cardiovascular diseases (N, %)	224 (52.1%)	57 (77.0%)	**<0.001**
Cerebrovascular diseases (N, %)[a]	2 (0.5%)	2 (2.7%)	0.195
Genetic profile			
Presence of APOE ε4 allele (N, %)	68 (23.8%)	13 (23.6)	0.982
Cognition at 3-year follow-up			
Change in MoCA score (median, IQR)	0 (-2–1)	-2 (-5–0.25)	**0.004**
Cognitive impairment (N, %)	46 (18.9)	22 (48.9%)	**<0.001**

[a]Correction for continuity was adapted for inadequate event.

Abbreviations: CSF, cerebrospinal fluid; DAT, dopaminergic transporter; IQR, interquartile range; MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Score part III; MoCA, Montreal Cognitive Assessment.

Table 2. Linear mixed model for interactive effect of CSF markers and BG-PVS on cognitive outcomes

	MoCA score at 3-year follow-up				Change in MoCA from baseline to 3-year follow-up			
	Model without interaction		Model with interaction		Model without interaction		Model with interaction	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
Model 1								
Baseline Aβ42/tTau	0.385 (0.153–0.617)	**0.001**	1.060 (0.619–1.500)	**<0.001**	0.382 (0.149–0.614)	**0.001**	1.055 (0.615–1.496)	**<0.001**
BG-PVS≥2	REF		REF				REF	
BG-PVS<2	1.283 (0.287–2.279)	**0.012**	6.000 (3.174–8.826)	**<0.001**	1.322 (0.326–2.318)	**0.010**	6.012 (3.187–8.836)	**<0.001**
Aβ42/tTau*BG-PVS interaction	/		-0.911 (-1.420—0.400)	**0.001**	/		-0.907 (-1.416–-0.397)	**0.001**
AIC	815.5		804.5		817.3		806.3	
Model 2								
Baseline Aβ42/pTau	0.031 (0.011–0.050)	**0.002**	0.092 (0.056–0.129)	**<0.001**	0.030 (0.011–0.050)	**0.003**	0.093 (0.056–0.129)	**<0.001**

BG-PVS≥2	REF		REF				REF	
BG-PVS<2	1.309 (0.267–2.350)	**0.014**	6.580 (3.740–9.419)	**<0.001**	1.359 (0317–2.400)	**0.011**	6.602 (3.763–9.441)	**<0.001**
$A\beta_{42}$/pTau*BG-PVS interaction			-0.08 (-0.13–-0.04)	**<0.001**			-0.084 (-0.126–-0.042)	**<0.001**
AIC	774.7		765.8		776.4		767.5	
Model 3								
Baseline $A\beta_{42}$	0.001 (0.000–0.002)	**0.035**	0.003 (0.001–0.005)	**0.004**	0.001 (0–0.002)	**0.038**	0.003 (0.001–0.005)	**0.004**
BG-PVS≥2	REF		REF				REF	
BG-PVS<2	1.258 (0.252–2.263)	**0.015**	3.184 (1.084–5.285)	**0.003**	1.326(0.321–2.330)	**0.010**	3.301 (1.207–5.396)	**0.002**
$A\beta_{42}$*BG-PVS interaction			-0.002 (-0.004–-0.000)	**0.039**			-0.002 (-0.004–0)	**0.035**
AIC	859.9		867.5		861.5		868.9	

CSF biomarkers ($A\beta_{42}$, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau), BG-PVS and their interaction were fixed effect. Age, baseline MoCA score, RBDSQ, and DAT putamen asymmetry were set as random effect for MoCA score at 3-year follow-up, and baseline sate trait anxiety inventory was additionally set as random effect for 3-year change in MoCA; Abbreviations:

AIC, Akaike information criterion; BG-PVS, basal ganglia perivascular space; REF, reference.

Perivascular Space in Parkinson's ~~disease~~Disease: Association with CSF Amyloid/Tau and Cognitive Ddecline

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Abstract

Objective: Whether perivascular space (PVS) visible on magnetic resonance imaging (MRI) represents glymphatic dysfunction and whether this imaging marker is pathologic in Parkinson's disease (PD) have been controversial. The objective was to determine whether PVS visible on MRI is independently associated with cognitive decline in patients with PD, and to test whether pathologic proteins in the CSF (such as $A\beta_{42}$) mediate the pathologic role of PVS.

Methods: A total of 341 patients with Parkinson's disease from Parkinson's Progression Marker Initiative (PPMI) cohort was included in the present study. PVS in the basal ganglia (BG-PVS) and centrum semiovale were evaluated with a semiquantitative scale. Changes in the Montreal Cognitive Assessment (MoCA) score and the absolute MoCA score at the 3-year assessment were considered the main cognitive outcome. A multivariable linear regression model was used to test the association between PVS and cognitive decline. A mixed linear model and path analysis were used to test the interaction among PVS, CSF biomarkers and cognitive decline.

Results: BG-PVS was associated with cognitive decline in patients with PD at the 3-year follow-up independent of age, baseline cognition, motor and nonmotor function, presynaptic dopaminergic deficiency, and CSF biomarkers. The interaction between BG-PVS and $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, and $A\beta_{42}$ levels was significantly predictive of 3-year cognitive decline. Path analysis confirmed that CSF $A\beta_{42}$/tTau levels partially mediated the pathologic effect of BG-PVS on cognitive outcome in PD.

Conclusions: BG-PVS is independently associated with cognitive decline in PD, and this association may be partially mediated by toxic CSF proteins.

Keywords: Parkinson's disease; Perivascular Space; Cognition; Amyloid; Tau

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with α-synuclein (α-syn) aggregation and Lewy body deposition being the pathologic hallmarks. Previous studies from several cohorts consistently reported that Alzheimer's disease (AD)-related CSF biomarkers (i.e., lower levels of $A\beta_{42}$ and $A\beta_{42}$/Tau ratios and higher levels of total and phosphorylated Tau) were associated with cognitive impairment in PD cross-sectionally[1-3] and longitudinally [1-3].

Emerging evidence has highlighted the role of the perivascular space (PVS) as a glymphatic pathway for waste clearance in the brain and demonstrated that glymphatic dysfunction reduced cerebrospinal fluid (CSF) clearance of Aβ in AD models and in patients with AD [4-6]. Since AD-related proteins are toxic to neurons and glial cells [7] and are associated with cognitive decline in AD and PD [1-3], it is possible that reduced CSF clearance of toxic proteins as a result of glymphatic dysfunction may aggregate the neurodegenerative process and facilitate the development of dementia. Indeed, patients with PD showed impaired meningeal lymphatic drainage assessed by dynamic contrast-enhanced magnetic resonance imaging (MRI), which may facilitate the α-syn deposition and result in motor dysfunction in PD mice model [8]. A previous cohort from Korea demonstrated that basal ganglia PVS (BG-PVS) visible on MRI predicted cognitive decline in PD at the 5-year follow-up [9][10]. This result needs to be validated in other cohorts. In addition, iIf BG-PVS visible on MRI reflects glymphatic dysfunction, there might be an association between the severity of BG-PVS visible on MRI and higher neurodegenerative burden measured by CSF biomarkers such as Aβ.

The Parkinson's Progression Marker Initiative (PPMI) is the largest ongoing cohort of PD with comprehensive clinical, imaging and CSF biomarker data. The PPMI provides an opportunity to confirm the pathologic role of BG-PVS in PD cognitive outcome. In addition, it provides superb data to test the relationship between PVS visible on MRI and neurodegenerative burden measured by CSF biomarkers, which may inform the mechanism and potential therapeutic target of PVS in progressive neurodegenerative processes. In the current analysis of PPMI data, we hypothesized that BG-PVS may be related with cognitive decline in PD, which may be mediated by CSF neurodegenerative biomarkers.

2. Method

2.1 Study design and participants

PPMI is an ongoing, multicenter, longitudinal, observational study that started in 2010 (https://www.ppmi-info.org/). Patients with early, drug-naïve PD and intact cognition were included. The PPMI study was approved by the institutional review board at each site, and participants provided written informed consent to participate. The protocol and more detailed study design of PPMI has been described elsewhere [9]. From the whole PPMI cohort, only PD patients with complete baseline BG-PVS profiles and CSF biomarkers were included in the present analysis. The data used in the current study were downloaded from the PPMI dataset in June 2020.

2.2 Outcome measurements

Cognitive decline was evaluated using the change in the MoCA score from baseline to 3-year follow-up and the absolute MoCA score at the 3-year assessment. ~~The Hopkins Verbal Learning Test (HVLT) (memory), the Benton Judgment of Line Orientation 15-item version (visuospatial function), the Symbol-Digit Modalities Test (processing speed), the Letter Number Sequencing (executive function and working memory), and the semantic (animal) fluency test (language) were also performed.~~ Motor function was measured using the Movement Disorder Society Unified Parkinson's Disease Rating

Scale (MDS-UPDRS) part III and Hoehn-Yahr stage. The MDS-UPDRS III score was further divided into four subscores according to the cardinal motor symptoms in PD: tremor (items 15-18), bradykinesia (items 4-8, and item14), rigidity (item 3), and axial signs (items 1, 2, 9-13). Nonmotor symptoms in the prediction of cognitive decline in PD included rapid eye movement behavior disorder (RBD), which was assessed with the RBD Screening Questionnaire (RBDSQ); sense of smell, which was assessed with the University of Pennsylvania Smell Identification Test (UPSIT); depression, which was assessed with the 15-item Geriatric Depression Scale (GDS); and anxiety, which was assessed with the State-Trait Anxiety Inventory.

2.3 DAT imaging

[123I]β-CIT DAT single-photon emission computed tomography (SPECT) imaging was acquired at PPMI imaging centers in accordance with the PPMI imaging protocol. Mean caudate and putaminal uptake relative to uptake in the occipital area and asymmetry of caudate and putaminal uptake (side with highest divided by side with lowest uptake) were computed for the analysis.

2.4 History of cardio- and cerebrovascular diseases and risk factors

Histories of cardio- and cerebrovascular diseases were recorded in the PPMI cohort at patient screening. Cardiovascular diseases ~~and risk factors~~ include a history of diabetes, hypertension, hyperlipidemia, hypercholesterolemia, and cardiac diseases. Cerebrovascular diseases included a history of cerebrovascular accident, transient ischemic attack, ischemic stroke, cervical and carotid stenosis or occlusion.

2.5 Imaging markers of cerebral small vessel disease

Imaging markers of cerebral small vessel disease (CSVD) were evaluated by a neurologist who was blind to the patient information (HJ Wan) following the instruction and definition of Standards for ReportIng Vascular changes on nEuroimaging (STRIVE) [10]. White matter hyperintensity (WMH) was rated according to the Fazekas rating scale [11]. Perivascular space was defined on MRI as small, sharply delineated structures of CSF intensity (or close to CSF intensity) following the course of perforating vessels. PVS in the basal ganglia and centrum semiovale (CS-PVS) were rated separately on T2 weighted sequence as 0 = none, 1 = 1–10, 2 = 11–20, 3 = 21–40, and 4 = >40 PVS per side, and the worse side was used if there was asymmetry [12, 13]. In the statistical analysis for BG-PVS, patients were stratified into groups with moderate-to-severe BG-PVS (BG-PVS rating≥2) and none-to-mild BG-PVS (BG-PVS rating<2). Similarly, in the analysis for WMH and CS-PVS, patients were also grouped into the high WMH group (Fazekas>2) versus the low WMH group (Fazekas≤2) and the high CS-PVS group (CS-PVS rating≥2) versus the low CS-PVS group (CS-PVS rating<2). This stratification was consistent with the distribution of CSVD profiles in our data and was consistent with studies showing that BG-PVS rating≥2 (moderate to severe) was predictive of unfavorable outcomes [12, 13].

2.6 Genotyping

At the screening visit, genomic DNA was extracted from whole blood of the subject. The APOE genotype was analyzed at the PPMI genetic core as previously described [14]. Subjects were classified by the presence or absence of *APOE* ε4 genotypes.

2.7 CSF biomarkers

The concentration of α-synuclein in CSF samples was analyzed using an ELISA assay available commercially from BioLegend. CSF $A\beta_{42}$, total tau (tTau) and tau phosphorylated at the threonine 181 position (pTau) were analyzed at Biorepository Core laboratories to the University of Pennsylvania using Elecsys electrochemiluminescence immunoassays (Roche Diagnostics). More detail and primary results of the measured CSF biomarkers have been reported previously in the PPMI cohort [14, 15].

2.8 Statistics

Continuous variables were compared between groups using the Mann-Whitney test (nonnormal distribution) or two sample t test (normal distribution), and categorical variables were compared between groups using the Chi-square test. Univariable~~te~~ and multivariable linear regression models were performed using the MoCA score at the 3-year follow-up and the 3-year change in the MoCA score as separate dependent variables. The regression models consulted a previous PPMI study using 2-year cognitive outcomes [16]. Multivariable regression models were conducted with adjustment of ~~V~~variables showing a ~~tendency to~~ significant association (p<0.05~~1~~) in the univariable regression analysis ~~further entered the multivariable linear regression analysis simultaneously, while(~~ only one significant variable of the same feature with lower P value was selected to avoid collinearity)~~.~~, and variables that showed significantly unbalanced features between BG-PVS groups. As CSF biomarkers were significantly correlated with each other (supplementary figure 1)[17], each biomarker entered the multivariable regression model separately.

The interaction between BG-PVS and CSF biomarkers in relation to cognition was firstly explored by plotting the fitting curve and then by linear mixed models. The change in MoCA score and MoCA score at the 3-year follow-up was used as dependent variables in linear mixed models~~,~~. BG-PVS severity and CSF biomarker with or without interaction term were set as fixed effects, and other variables showing significant association with cognitive outcomes in ~~multivariable~~ univariable regression ~~and~~or unbalanced features between BG-PVS groups were used as random effects. The Akaike information criterion (AIC) of models with and without the BG-PVS*CSF biomarker interaction item was recorded. Path analysis was conducted to investigate how much CSF biomarkers mediated the effect of BG-PVS on cognition in PD. The standardized coefficient (β) of BG-PVS without a mediation effect (direct effect) and with a mediation effect (indirect effect) and the standardized coefficient (β) of the CSF biomarker on the change in MoCA were calculated. P value < 0.05 was defined as significant. Group comparison of CSF biomarkers at each follow-up point was also performed between PD groups with different BG-PVS severities. P value < 0.01 was defined as significant in this group comparison for multiple comparison correction (~~Bonferroni~~ correction for 4 repeated comparisons for each CSF biomarker). Group comparison was conducted in SPSS 25.0 (SPSS, inc., Beijing, China), and linear regression and linear mixed models were performed in R software version 4.02 (https://www.r-project.org/).

To rule out confounding by ~~other CSVD markers~~ WMH and lacune, –and to investigate the location specificity of PVS, their relationships ~~among (~~WMH, the presence of lacune or CS-PVS), with CSF biomarkers~~,~~ and cognitive decline were~~as~~ further explored using a similar statistical approach.

2.9 Data Availability Statement

The data was publicly available on PPMI website (https://www.ppmi-info.org/access-data-specimens/).

3. Results

3.1 Baseline features of the included patients

Four hundred and twenty-three patients with drug-naïve PD were recruited in PPMI cohort. Among these subjects, MRI imaging or T2-weighted imaging was missing in 47 patients, and imaging in another 13 patients was not qualified to rate BG-PVS due to incomplete or nonaxial slices. CSF biomarkers were missing in another 22 patients with PD. Finally, 341 patients with complete baseline

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PVS and CSF biomarkers were included in the present analysis. The included and excluded patients showed overall similar demographic and behavioral profiles (supplementary table 1).

3.2 Group comparison between patients with lower and higher BG-PVS burdens

Compared with patients with lower BG-PVS burden, patients with more severe BG-PVS were significantly older; had more impaired motor function at baseline; had a higher prevalence of previous cardiovascular disease; had a higher prevalence of and the presence of lacune presence, and more severe WMH at baseline; had a higher risk of cognitive impairment and a greater decline in the MoCA score at the 3-year follow-up despite of similar baseline MoCA scores; and showed lower levels of CSF $A\beta_{42}$α-synuclein, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau and higher levels of CSF α-syn, tTau and pTau at baseline (**Table 1**).

3.3 Univariate Univariable linear regression for cognition at the 3-year follow-up

Using the absolute MoCA score at the 3-year follow-up as the dependent variable, age, baseline MoCA score, MDS-UPDRS III total score, tremor, bradykinesia, and axial subscores, RBDSQ, UPSIT score, CSF $A\beta_{42}$, tTau, pTau, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, putamen asymmetry and BG-PVS were significantly associated with cognition at the 3-year follow-up in PD patients ($P<0.05$).

Using decline in MoCA score as the dependent variable, age, baseline MoCA score, RBDSQ, UPSIT score, axial subscore of MDS-UPDRS III, CSF $A\beta_{42}$, tTau, pTau, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, putamen asymmetry, and BG-PVS were significantly associated with cognitive decline during three years in PD patients ($P<0.05$) (supplementary table 2).

3.4 ***Multivariable linear regression for cognition at the 3-year follow-up***

In multivariable regression models, BG-PVS was significantly associated with MoCA score or change in MoCA score, independent of age, past -history cardiovascular diseases, baseline MoCA score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, putamen asymmetry, WMH Fazekas score, and the presence of lacunes, and CSF biomarkers. Age, baseline cognition, motor function, nonmotor symptoms, presynaptic dopaminergic deficiency, and CSF biomarkers. Baseline CSF Aβ_{42}, Aβ_{42}/tTau and Aβ_{42}/pTau were significantly associated with the MoCA score or change in the MoCA score at 3-year follow-up independent of age, past history cardiovascular diseases, baseline MoCA score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, putamen asymmetry, WMH Fazekas score, the presence of lacune, and BG-PVSCSF biomarkers.age, baseline cognition, motor function, nonmotor symptoms, presynaptic dopaminergic deficiency, and BG-PVS. However, baseline CSF tTau and pTau were not significantly associated with either cognitive outcome at year three after adjustment (supplementary table 3).

3.5 ***Interaction between CSF biomarkers and BG-PVS***

There was a significant main effect of BG-PVS and CSF Aβ_{42}/tTau, Aβ_{42}/pTau and Aβ_{42} as well as interactions between BG-PVS and these CSF biomarkers (**Table 2**), such that patients with higher BG-PVS and lower Aβ_{42}/tTau (**Figure 1A**), Aβ_{42}/pTau (**Figure 1B**), or Aβ_{42} (**Figure 1C**) showed steeper decline in the MoCA score at the 3-year follow-up. Models containing interaction terms provided a slightly improved fit. As patients with a higher BG-PVS burden had a higher prevalence of cardiovascular disease and risk factors, we further tested whether the interaction between BG-PVS and CSF biomarkers was confounded by the presence of cardiovascular disease and risk factors. However, the correlation between CSF biomarkers and cognitive decline was not stratified by the presence of cardiovascular disease or related risk factors (supplementary figure 2).

We further compared CSF biomarkers at each follow-up timepoint between the BG-PVS groups. The results revealed that patients with more severe BG-PVS showed significantly higher levels of all measured CSF biomarkers at baseline, 1-year follow-up, and 2-year follow-up, and the significant difference in tTau and pTau was still observed at year three (supplementary table 4 4) with corrected P values (P<0.01) (supplementary table 4).

3.6 ***Path analysis***

In path analysis, CSF $A\beta_{42}$/tTau was found to mediate the effect of BG-PVS on cognitive decline (total effect [original coefficient] = -0.256, direct effect [corrected coefficient] = -0.208, indirect effect = -0.048) (**Figure 2A**). That is, CSF $A\beta_{42}$/tTau mediated 18.8% (indirect effect/total effect) of the BG-PVS effect on the decrease in MoCA scores during the 3-year follow-up. In path analysis, the correlation of BG-PVS with $A\beta_{42}$/pTau was marginally significant, and that with $A\beta_{42}$ was not significant (**Figure 2B and 2C**).

3.7 ***Additional analysis with WMH and CS-PVS***

To rule out the confounding effect of WMH, lacune and CS-PVS, additional analysis was performed. No significant association was found among WMH, CSF biomarkers, and cognitive outcome; among the presence of lacune, CSF biomarkers, and cognitive outcome; and among CS-PVS, CSF biomarkers, and cognitive outcome (see supplementary figure 3 and supplementary result). For WMH, no significant difference in baseline CSF biomarkers (α-syn z = -1.337, P = 0.181; $A\beta_{42}$ z = -0.430, P = 0.667; pTau z = -1.181, P = 0.238; tTau z = -1.697, P = 0.090) was found between groups with different WMH severity (Fazekas 0-2 vs. Fazekas 3-6). No significant correlation was found between CSF biomarkers and WMH Fazekas rating according to the Spearman correlation analysis (α-syn r = 0.025, P = 0.640; $A\beta_{42}$ r = -0.057, P = 0.300; pTau r = 0.036, P = 0.534; tTau r = 0.039, P = 0.331). No significant correlation was observed between WMH and cognitive decline or between WMH and CSF biomarkers ($A\beta_{42}$/tTau, $A\beta_{42}$/pTau, $A\beta_{42}$) in the path analysis (supplementary figure 3).

For CS-PVS, no significant difference in baseline CSF biomarkers (α-syn z = -1.391, P = 0.164; $A\beta_{42}$ z = -0.685, P = 0.493; pTau z = -1.422, P = 0.155; tTau z = -1.741, P = 0.082) was found between groups stratified by CS-PVS severity (CS-PVS 0-1 vs. CS-PVS≥2). No significant correlation was observed between CS-PVS and CSF biomarkers ($A\beta_{42}$/tTau, $A\beta_{42}$/pTau, $A\beta_{42}$) in path analysis (supplementary figure 3). Although a marginally significant correlation between CS-PVS and cognitive decline was observed in the path analysis, the significant correlation was not preserved in the multivariable linear model adjusting for age (coefficient = -0.729, 95% CI = -1.612–0.154, P = 0.105) or in the model adjusted for age, baseline MoCA scores, baseline state trait anxiety score, RBDSQ, UPSIT, and putamen asymmetry (coefficient = -0.615, 95% CI = -1.419–0.188, P = 0.132).

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4. Discussion

This is the first study that examined the relationship between among CSF biomarkers-, cognitive outcome and PVS visible on MRI in neurodegenerative diseasePD. The main finding demonstrated that BG-PVS was independently associated with cognitive decline in patients with PD. In addition, BG-PVS modified the pathologic effect of $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, and $A\beta_{42}$ on cognitive decline in PD. Path analysis confirmed that CSF biomarkers, especially $A\beta_{42}$/tTau, partially mediated the pathologic effect of BG-PVS on cognitive outcomes in PD. These results suggest that the increased visibility of BG-PVS on MRI may reflect more advanced glymphatic dysfunction, resulting in higher levels of toxic CSF proteins, which may in turn accelerate neurodegenerative processes and cognitive decline. It also implies that the glymphatic pathway may serve as a therapeutic target to preserve cognition in neurodegenerative disease.

Our results validated a previous study by Park and colleagues and showed that BG-PVS was

~~associated with 3-year cognitive decline in patients with PD~~ [18], and showed that BG-PVS was associated with 3-year cognitive decline in patients with PD. In addition, the contribution to poor cognitive outcome and the interaction with CSF proteins were specific for PVS located in the basal ganglia but not the centrum semiovale. However, the underlying mechanism for the location specificity remains unclear. Evidence suggests that cerebral arterial pulsation drove CSF-interstitial fluid exchange mediated by the glymphatic pathway [19], and arterial stiffness was associated with a higher BG-PVS burden [20]. It is possible that PVS in the basal ganglia may be more prone to arterial damage and pulsation change during aging. However, we did not test arterial function, such as arterial stiffness and regulation. Future studies will be needed to test this hypothesis. In addition, BG-PVS differs from CS-PVS in structure, as BG-PVS is covered by two leptomeningeal membranes and directly connects CSF [21]. This means that BG-PVS may be more active in eliminating waste from CSF, and the increased visibility of BG-PVS may represent an increased effort in waste clearance. Future studies directly comparing CSF dynamics are needed to investigate the location difference of PVS.

Moreover, the results ~~also~~ suggested that PVS visible on MRI may reflect glymphatic dysfunction, ~~and~~ impaired~~ed~~ efflux of CSF proteins and more advanced neurodegeneration in patients with PD. Previous evidence suggested that patients with PD showed higher volume fraction of PVS, especially for~~in~~ those familial patients with genetic mutation [22]. Previous PPMI ~~result~~data also suggested that PVS in midbrain was associated ~~other~~ neurodegenerative imaging marker ~~–~~ (DAT deficiency) [23]. These findings support~~ed~~ our hypothesis that PVS visible on MRI may be closely linked with neurodegeneration in patients with PD. We found that ~~In addition,~~ the level of neurodegenerative CSF proteins ($A\beta_{42}$/tTau) partially mediated the effect of BG-PVS on poor cognitive outcome. Taking that CSF proteins, including Aβ and Tau, are toxic to neurons and glial cells [7] and AD biomarkers are predictive of cognitive decline in PD [1-3], the result implies that BG-PVS may contribute to cognitive decline by elevating toxic CSF proteins in patients with PD.

The glymphatic pathway has drawn much attention in recent years as a novel pathway to exclude neurotoxic proteins and a potential therapeutic target [24]. In patients with superficial sclerosis, PVS was enlarged beneath the affected area where Aβ was deposited in the cortical arterial wall by biopsy, supporting the notion that enlarged PVS is a sign of a blocked drainage pathway by proteins such as Aβ [25]. Ding and colleagues specifically tested the meningeal lymphatic flow in patients with PD using dynamic contrast-enhanced MRI, and proved significant reduction of lymphatic flow as well as notable delay in deep cervical lymph node perfusion in these patients. In addition, the delayed meningeal lymphatic drainage was followed by α-syn pathology in mice model [8, 22]. This study provided direct evidence of impaired glymphatic system in PD and the consequent neurodegeneration (e.g. α-syn pathology). Therefore, PVS visible on routine MRI may be an alternative a possible way to explore the static glymphatic pathway offline. [26, 27]

In PD patients with higher BG-PVS burden, CSF α-syn, tTau and pTau levels were higher, while the CSF $A\beta_{42}$ level was lower compared with patients with mild or none BG-PVS. Hypothetically, reduced efflux as a result glymphatic dysfunction should cause increased CSF protein level. As for $A\beta_{42}$, it is possible that the decreased CSF $A\beta_{42}$ reflected more extensive peptide aggregation and plaque formation in brain tissue [30]. Tau and Aβ have independent as well as synergistic effects on cognition [26]. In our analysis, the interaction between CSF biomarker and BG-PVS was more predominant for $A\beta_{42}$/tTau, and $A\beta_{42}$/pTau, compared with $A\beta_{42}$ alone. It is possible that glymphatic dysfunction blocked CSF toxic proteins, and the interaction between these increased proteins (e.g. Tau-$A\beta_{42}$ interaction) accelerated the aggregation of amyloid, lowering the amounts of $A\beta_{42}$ being tested in

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CSF.

CSF $A\beta_{42}$, $A\beta_{42}$/tTau, and $A\beta_{42}$/pTau were not specific PD biomarkers. However, emerging evidence suggests that concurrent proteinopathies and their synergistic interactions, are quite common and may contribute to cognitive decline in patients with PD [27]. There might be concomitant AD pathology playing a role in our findings. Previous studies suggested that PVSs in the centrum semiovale and hippocampus were as associated with the diagnosis of AD [28, 29], and PVSs in the hippocampus was associated with hippocampal atrophy[29]. However, the association between PVS visible on MRI and CSF biomarkers was not statistically significant in cognitively impaired individuals in Neurodegenerative Disorders Early and Reliably (BioFINDER) study [29]. More studies are needed to test the association between PVS visible on MRI and CSF biomarkers in demented and non-demented populations.

The interactive effect between BG-PVS and CSF $A\beta_{42}$, $A\beta_{42}$/tTau, and $A\beta_{42}$/pTau on cognitive decline was a novel finding in our study. This suggests that modification of the glymphatic pathway may be a potential and crucial therapeutic target to alleviate the pathologic effect of $A\beta_{42}$ and Tau on cognitive decline in PD. Emerging evidence has demonstrated the interaction between PVS and AD-related proteins in animal models[28], and our result further supported the additive consequence of their interaction in human cohort. In addition, the benefit of treatment targeting the glymphatic pathway may be beyond AD-related pathology since PVS has also been highlighted to be involved in the inflammatory process in multiple sclerosis [36] Sleep intervention may be an effective way to improve glymphatic function, which may need to be tested in clinical trials or observational studies [37]. Other treatments targeting pericytes, endothelial cells, perivascular inflammation and other factors pertaining to glymphatic function also deserve to be investigated.

In addition to our initial hypothesis, the factors associated with 3-year cognitive decline were largely consistent with previous 2-year follow-up analysis [16]. More recently, Irwin and colleagues reported that AD-related CSF biomarkers were associated with 3-year cognitive decline in a PPMI cohort [17]. Although finding risk factors associated with cognitive decline was not the main topic of our study, the consistency with previous data suggests that the present data are representative of the whole cohort despite missing BG-PVS data in 59 patients (missing rate = 13.9%).

We acknowledge several limitations. First, this study did not measure the dynamic function of the glymphatic pathway in vivo. Currently, dynamic fluid exchange by the glymphatic pathway has been investigated in vivo by intrathecal injection of the contrast agent in neurological diseases such as idiopathic normal pressure hydrocephalus [6]. These approaches enable tracking uptake and distribution of tracers dynamically, but they are invasive and may not be applicable in patients with PD. Second, although CSF $A\beta_{42}$ and Tau are consistently found to be associated with cognitive decline in PD, they are not PD-specific biomarkers. In addition, the findings of the present study only represent the PD population. Whether proteinaceous waste such as Aβ and Tau drives the increased visibility of PVS on MRI and potentially mediates its toxicity needs to be tested in the AD population and normal aging population.

In conclusion, we found that BG-PVS may be independently associated with cognitive decline in PD, which may be partially mediated by toxic CSF proteins. The increased visibility of BG-PVS on MRI may reflect more advanced glymphatic dysfunction. PVS may serve as a therapeutic target to preserve cognition in PD.

Conflict of interest

None

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Figure legends

Figure 1. Correlation between CSF biomarkers and cognitive outcomes stratified by BG-PVS

BG-PVS modified the effect of Aβ_{42}/tTau (A), Aβ_{42}/pTau (B), Aβ_{42} (C) on cognitive outcome in Parkinson's disease, as high BG-PVS group showed steeper decline in the MoCA score in relation to CSF biomarkers at the 3-year follow-up.

Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid.

Figure 2. Path analysis

A. CSF Aβ_{42}/tTau, but not Aβ_{42}/pTau or CSF Aβ_{42} significantly mediated the effect of BG-PVS on cognitive decline in patients with PD. The effect of WMH (B) or CS-PVS (C) on cognitive outcome was not mediated by CSF biomarkers.

Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid; WMH, white matter hyperintensity.

Supplementary figures:

FIG. S1. Correlation between CSF biomarkers

Abbreviations: CSF, cerebrospinal fluid.

FIG. S2. Correlation between CSF biomarkers and cognitive decline stratified by the presence of cardiovascular disease

The presence of cardiovascular disease did not modify the effect of CSF biomarkers on cognitive decline in patients with PD.

FIG. S3. Path analysis for WMH, CS-PVS and CSF biomarkerlacune, and CS-PVSs

CSF biomarkers did not mediate the effect of WMH, the presence of lacune or CS-PVS on cognitive decline in PD.

Table 1. Demographic information between groups stratified by BG-PVS

	PD with low BG-PVS (N = 286)	PD with high BG-PVS (N = 55)	P value
Demographic			
Age (median, IQR, year)	60.7 (53.5–66.6)	71.1 (67.1–74.8)	**<0.001**
Gender (F/M)	100/186~~8~~	15/40	0.269
Disease profile			
Disease duration (median, IQR, month)	4 (2–7)	6 (3–13)	0.066
MoCA Score (median, IQR)	28 (26–29)	27 (25–29)	0.222
Hoehn-Yahr staging (median, IQR)	2 (1–2)	2 (2–2)	**0.001**
MDS-UPDRS III total (median, IQR)	19 (14–26)	22 (16–27)	**0.024**
Tremor subscore (median, IQR)	5 (2–8)	6 (2–9)	0.117
Bradykinesia subscore (median, IQR)	11 (6–15)	14 (9–19)	**0.008**
Axial subscore (median, IQR)	4 (2–5)	4 (3–7)	**0.008**
Rigidity subscore (median, IQR)	4 (2–6)	5 (3–9)	**0.031**
State Trait Anxiety Score (median, IQR)	94 (89–98)	94 (88–97)	0.500
Geriatric Depression Scale (median, IQR)	5 (5–6)	5 (4–6)	0.280
CSF biomarkers			
CSF α-synuclein (median, IQR, pg/ml)	1351.3 (1029.3–1718.0)	1528.8 (1164.3–2086.0)	**0.016**
CSF Aβ_{42} (median, IQR, pg/mL)	848.6 (615.1–1119.0)	822.2 (627.9–1050.5)	0.860

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CSF pTau (median, IQR, pg/mL)	13.0 (10.9–16.7)	15.4 (12.4–21.4)	**0.001**
CSF tTau (median, IQR, pg/mL)	152.6 (124.0–192.6)	186.4 (147.2–237.7)	**<0.001**
CSF $A\beta_{42}$/tTau	5.81 (4.69–6.69)	4.88 (3.71–6.01)	**0.002**
CSF $A\beta_{42}$/pTau	69.4 (57.4–80.3)	61.1 (42.7–75.7)	**0.002**
DAT striatal binding ratios			
Mean caudate uptake (median, IQR)	2.02 (1.67–2.37)	1.88 (1.54–2.21)	0.155
Mean putamen uptake (median, IQR)	1.79 (1.48–2.18)	1.77 (1.34–2.08)	0.270
Caudate asymmetry (median, IQR)	1.19 (1.10–1.31)	1.17 (1.07–1.27)	0.216
Putamen asymmetry (median, IQR)	1.45 (1.19–1.76)	1.39 (1.17–1.73)	0.484
Small vessel disease profile			
WMH Fazekas score (median, IQR)	2 (1–2)	3 (2–4)	**<0.001**
The presence of lacunes (N, %)	145 (50.7%)	45 (81.8%)	**<0.001**
Cardiovascular diseases (N, %)	224 (52.1%)	57 (77.0%)	**<0.001**
Cerebrovascular diseases (N, %)[a]	2 (0.5%)	2 (2.7%)	0.195
Genetic profile			
Presence of APOE ε4 allele (N, %)	68 (23.8%)	13 (23.6)	0.982
Cognition at 3-year follow-up			
Change in MoCA score (median, IQR)	0 (-2–1)	-2 (-5–0.25)	**0.004**
Cognitive impairment (N, %)	46 (18.9)	22 (48.9%)	**<0.001**

[a]Correction for continuity was adapted for inadequate event.

Abbreviations: CSF, cerebrospinal fluid; DAT, dopaminergic transporter; IQR, interquartile range; MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Score part III; MoCA, Montreal Cognitive Assessment.

Table 2. Linear mixed model for interactive effect of CSF markers and BG-PVS on cognitive outcomes

	MoCA score at 3-year follow-up				Change in MoCA from baseline to 3-year follow-up			
	Model without interaction		Model with interaction		Model without interaction		Model with interaction	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
Model 1								
Baseline $A\beta_{42}$/tTau	0.385 (0.154–0.617)0.385 (0.153–0.617)	**0.0010.001**	1.087 (0.650–1.524)1.060 (0.619–1.500)	**<0.001<0.001**	0.388 (0.156–0.619)0.382 (0.149–0.614)	**0.0010.001**	1.086 (0.649–1.523)1.055 (0.615–1.496)	**<0.001<0.001**
BG-PVS≥2	REF		REFREF		REF		REFREF	
BG-PVS<2	1.302 (0.271–2.334)1.283 (0.287–2.279)	**0.0140.012**	6.364 (3.515–9.214)6.000 (3.174–8.826)	**<0.001<0.001**	1.317 (0.285–2.349)1.322 (0.326–2.318)	**0.0130.010**	6.357 (3.507–9.207)6.012 (3.187–8.836)	**<0.001<0.001**
$A\beta_{42}$/tTau*BG-PVS	/		-0.953 (-1.460–-	**<0.0010.001**	//		-0.949 (-1.456–-0.441)-	**<0.0010.001**

interaction			0.445)-0.911 (-1.420–-0.400)				-0.907 (-1.416–-0.397)	
AIC	823.4815.5		811.4804.5		823.2817.3		811.3806.3	
Model 2								
Baseline Aβ_{42}/pTau	0.031 (0.011–0.050)0.031 (0.011–0.050)	**0.0020.002**	0.095 (0.059–0.131)0.092 (0.056–0.129)	**<0.001<0.001**	0.031 (0.011–0.050)0.030 (0.011–0.050)	**0.0020.003**	0.095 (0.059–0.131)0.093 (0.056–0.129)	**<0.001<0.001**
BG-PVS≥2	REFREF		REFREF		REF		REFREF	
BG-PVS<2	1.364 (0.282–2.445)1.309 (0.267–2.350)	**0.0140.014**	7.040 (4.170–9.909)6.580 (3.740–9.419)	**<0.001<0.001**	1.387 (0.305–2.468)1.359 (0317–2.400)	**0.0130.011**	7.057 (4.186–9.927)6.602 (3.763–9.441)	**<0.001<0.001**
Aβ_{42}/pTau*BG-PVS interaction	/		-0.088 (-0.130–-0.046)-0.08 (-0.13–	**<0.001<0.001**	/		-0.088 (-0.130–-0.046)-0.084 (-0.126–-0.042)	**<0.001<0.001**

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			~~0.04)~~					
AIC	782.6~~774.7~~		~~765.8~~772.5		782.4~~776.4~~		772.3~~767.5~~	
Model 3								
Baseline $A\beta_{42}$	0.001 (0–0.002)~~0.001 (0.000–0.002)~~	**0.033~~0.035~~**	0.003 (0.001–-0.005)~~0.003 (0.001–0.005)~~	**0.003~~0.004~~**	0.001 (0–0.002)~~0.001 (0–0.002)~~	**0.034~~0.038~~**	0.003 (0.001–0.005)~~0.003 (0.001–0.005)~~	**0.003~~0.004~~**
BG-PVS≥2	REF~~REF~~		REF~~REF~~		REF		REF~~REF~~	
BG-PVS<2	1.286 (0.253–2.318)~~1.258 (0.252–2.263)~~	**0.015~~0.015~~**	3.328 (1.224–5.432)~~3.184 (1.084–5.285)~~	**0.002~~0.003~~**	1.299 (0.266–2.331)~~1.326(0.321–2.330)~~	**0.014~~0.010~~**	3.326 (1.221–5.430)~~3.301 (1.207–5.396)~~	**0.002~~0.002~~**
$A\beta_{42}$*BG-PVS interaction	/		-0.002 (-0.004–0)~~-0.002 (-0.004–0.000)~~	**0.029~~0.039~~**	/		-0.002 (-0.004–0)~~-0.002 (-0.004–0)~~	**0.030~~0.035~~**
AIC	867.6~~859.9~~		~~867~~874.8~~.5~~		867.9~~861.5~~		875.2~~868.9~~	

CSF biomarkers (Aβ_{42}, Aβ_{42}/tTau, Aβ_{42}/pTau), BG-PVS and their interaction were fixed effect; aAge, baseline MoCA score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, and putamen asymmetry, WMH Fazekas score, the presence of lacunes, past history cardiovascular diseases were set as random effect.CSF biomarkers (Aβ_{42}, Aβ_{42}/tTau, Aβ_{42}/pTau), BG-PVS and their interaction were fixed effect. Age, baseline MoCA score, RBDSQ, and DAT putamen asymmetry were set as random effect for MoCA score at 3-year follow-up, and baseline sate trait anxiety inventory was additionally set as random effect for 3-year change in MoCA; Abbreviations: AIC, Akaike information criterion; BG-PVS, basal ganglia perivascular space; REF, reference.

Perivascular Space in Parkinson's Disease: Association with CSF Amyloid/Tau and Cognitive Decline

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Abstract

Objective: Whether perivascular space (PVS) visible on magnetic resonance imaging (MRI) represents glymphatic dysfunction and whether this imaging marker is pathologic in Parkinson's disease (PD) have been controversial. The objective was to determine whether PVS visible on MRI is independently associated with cognitive decline in patients with PD, and to test whether pathologic proteins in the CSF (such as $A\beta_{42}$) mediate the pathologic role of PVS.

Methods: A total of 341 patients with Parkinson's disease from Parkinson's Progression Marker Initiative (PPMI) cohort was included in the present study. PVS in the basal ganglia (BG-PVS) and centrum semiovale were evaluated with a semiquantitative scale. Changes in the Montreal Cognitive Assessment (MoCA) score and the absolute MoCA score at the 3-year assessment were considered the main cognitive outcome. A multivariable linear regression model was used to test the association between PVS and cognitive decline. A mixed linear model and path analysis were used to test the interaction among PVS, CSF biomarkers and cognitive decline.

Results: BG-PVS was associated with cognitive decline in patients with PD at the 3-year follow-up independent of age, baseline cognition, motor and nonmotor function, presynaptic dopaminergic deficiency, and CSF biomarkers. The interaction between BG-PVS and $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, and $A\beta_{42}$ levels was significantly predictive of 3-year cognitive decline. Path analysis confirmed that CSF $A\beta_{42}$/tTau levels partially mediated the pathologic effect of BG-PVS on cognitive outcome in PD.

Conclusions: BG-PVS is independently associated with cognitive decline in PD, and this association may be partially mediated by toxic CSF proteins.

Keywords: Parkinson's disease; Perivascular Space; Cognition; Amyloid; Tau

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with α-synuclein (α-syn) aggregation and Lewy body deposition being the pathologic hallmarks. Previous studies from several cohorts consistently reported that Alzheimer's disease (AD)-related CSF biomarkers (i.e., lower levels of $A\beta_{42}$ and $A\beta_{42}$/Tau ratios and higher levels of total and phosphorylated Tau) were associated with cognitive impairment in PD [1-3].

Emerging evidence has highlighted the role of the perivascular space (PVS) as a glymphatic pathway for waste clearance in the brain and demonstrated that glymphatic dysfunction reduced cerebrospinal fluid (CSF) clearance of Aβ in AD models and in patients with AD [4-6]. Since AD-related proteins are toxic to neurons and glial cells [7] and are associated with cognitive decline in AD and PD [1-3], it is possible that reduced CSF clearance of toxic proteins as a result of glymphatic dysfunction may aggregate the neurodegenerative process and facilitate the development of dementia. Indeed, patients with PD showed impaired meningeal lymphatic drainage assessed by dynamic contrast-enhanced magnetic resonance imaging (MRI), which may facilitate the α-syn deposition and result in motor dysfunction in PD mice model [8]. If BG-PVS visible on MRI reflects glymphatic dysfunction, there might be an association between the severity of BG-PVS visible on MRI and higher neurodegenerative burden measured by CSF biomarkers such as Aβ.

The Parkinson's Progression Marker Initiative (PPMI) is the largest ongoing cohort of PD with comprehensive clinical, imaging and CSF biomarker data. The PPMI provides an opportunity to confirm the pathologic role of BG-PVS in PD cognitive outcome. In addition, it provides superb data to test the relationship between PVS visible on MRI and neurodegenerative burden measured by CSF biomarkers, which may inform the mechanism and potential therapeutic target of PVS in progressive neurodegenerative processes. In the current analysis of PPMI data, we hypothesized that BG-PVS may be related with cognitive decline in PD, which may be mediated by CSF neurodegenerative biomarkers.

2. Method

2.1 Study design and participants

PPMI is an ongoing, multicenter, longitudinal, observational study that started in 2010 (https://www.ppmi-info.org/). Patients with early, drug-naïve PD and intact cognition were included. The PPMI study was approved by the institutional review board at each site, and participants provided written informed consent to participate. The protocol and more detailed study design of PPMI has been described elsewhere [9]. From the whole PPMI cohort, only PD patients with complete baseline BG-PVS profiles and CSF biomarkers were included in the present analysis. The data used in the current study were downloaded from the PPMI dataset in June 2020.

2.2 Outcome measurements

Cognitive decline was evaluated using the change in the MoCA score from baseline to 3-year follow-up and the absolute MoCA score at the 3-year assessment. Motor function was measured using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III and Hoehn-Yahr stage. The MDS-UPDRS III score was further divided into four subscores according to the cardinal motor symptoms in PD: tremor (items 15-18), bradykinesia (items 4-8, and item14), rigidity (item 3), and axial signs (items 1, 2, 9-13). Nonmotor symptoms in the prediction of cognitive decline in PD included rapid eye movement behavior disorder (RBD), which was assessed with the RBD Screening Questionnaire (RBDSQ); sense of smell, which was assessed with the University of Pennsylvania Smell Identification Test (UPSIT); depression, which was assessed with the 15-item

Geriatric Depression Scale (GDS); and anxiety, which was assessed with the State-Trait Anxiety Inventory.

2.3 DAT imaging

[123I]β-CIT DAT single-photon emission computed tomography (SPECT) imaging was acquired at PPMI imaging centers in accordance with the PPMI imaging protocol. Mean caudate and putaminal uptake relative to uptake in the occipital area and asymmetry of caudate and putaminal uptake (side with highest divided by side with lowest uptake) were computed for the analysis.

2.4 History of cardio- and cerebrovascular diseases and risk factors

Histories of cardio- and cerebrovascular diseases were recorded in the PPMI cohort at patient screening. Cardiovascular diseases include a history of diabetes, hypertension, hyperlipidemia, hypercholesterolemia, and cardiac diseases. Cerebrovascular diseases included a history of cerebrovascular accident, transient ischemic attack, ischemic stroke, cervical and carotid stenosis or occlusion.

2.5 Imaging markers of cerebral small vessel disease

Imaging markers of cerebral small vessel disease (CSVD) were evaluated by a neurologist who was blind to the patient information (HJ Wan) following the instruction and definition of Standards for ReportIng Vascular changes on nEuroimaging (STRIVE) [10]. White matter hyperintensity (WMH) was rated according to the Fazekas rating scale [11]. Perivascular space was defined on MRI as small, sharply delineated structures of CSF intensity (or close to CSF intensity) following the course of perforating vessels. PVS in the basal ganglia and centrum semiovale (CS-PVS) were rated separately on T2 weighted sequence as 0 = none, 1 = 1–10, 2 = 11–20, 3 = 21–40, and 4 = >40 PVS per side, and the worse side was used if there was asymmetry [12, 13]. In the statistical analysis for BG-PVS, patients were stratified into groups with moderate-to-severe BG-PVS (BG-PVS rating≥2) and none-to-mild BG-PVS (BG-PVS rating<2). Similarly, in the analysis for WMH and CS-PVS, patients were also grouped into the high WMH group (Fazekas>2) versus the low WMH group (Fazekas≤2) and the high CS-PVS group (CS-PVS rating≥2) versus the low CS-PVS group (CS-PVS rating<2). This stratification was consistent with the distribution of CSVD profiles in our data and was consistent with studies showing that BG-PVS rating≥2 (moderate to severe) was predictive of unfavorable outcomes [12, 13].

2.6 Genotyping

At the screening visit, genomic DNA was extracted from whole blood of the subject. The APOE genotype was analyzed at the PPMI genetic core as previously described [14]. Subjects were classified by the presence or absence of *APOE* ε4 genotypes.

2.7 CSF biomarkers

The concentration of α-synuclein in CSF samples was analyzed using an ELISA assay available commercially from BioLegend. CSF $A\beta_{42}$, total tau (tTau) and tau phosphorylated at the threonine 181 position (pTau) were analyzed at Biorepository Core laboratories to the University of Pennsylvania using Elecsys electrochemiluminescence immunoassays (Roche Diagnostics). More detail and primary results of the measured CSF biomarkers have been reported previously in the PPMI cohort [14, 15].

2.8 Statistics

Continuous variables were compared between groups using the Mann-Whitney test (nonnormal distribution) or two sample t test (normal distribution), and categorical variables were compared between groups using the Chi-square test. Univariable and multivariable linear regression models were performed using the MoCA score at the 3-year follow-up and the 3-year change in the MoCA score as separate dependent variables. The regression models consulted a previous PPMI study using 2-year cognitive outcomes [16]. Multivariable regression models were conducted with adjustment of variables showing a significant association ($p<0.05$) in the univariable regression analysis (only one significant variable of the same feature with lower P value was selected to avoid collinearity), and variables that showed significantly unbalanced features between BG-PVS groups. As CSF biomarkers were significantly correlated with each other (supplementary figure 1)[17], each biomarker entered the multivariable regression model separately.

The interaction between BG-PVS and CSF biomarkers in relation to cognition was firstly explored by plotting the fitting curve and then by linear mixed models. The change in MoCA score and MoCA score at the 3-year follow-up was used as dependent variables in linear mixed models. BG-PVS severity and CSF biomarker with or without interaction term were set as fixed effects, and other variables showing significant association with cognitive outcomes in univariable regression or unbalanced features between BG-PVS groups were used as random effects. The Akaike information criterion (AIC) of models with and without the BG-PVS*CSF biomarker interaction item was recorded. Path analysis was conducted to investigate how much CSF biomarkers mediated the effect of BG-PVS on cognition in PD. The standardized coefficient (β) of BG-PVS without a mediation effect (direct effect) and with a mediation effect (indirect effect) and the standardized coefficient (β) of the CSF biomarker on the change in MoCA were calculated. P value < 0.05 was defined as significant. Group comparison of CSF biomarkers at each follow-up point was also performed between PD groups with different BG-PVS severities. P value < 0.01 was defined as significant in this group comparison for multiple comparison correction (correction for 4 repeated comparisons for each CSF biomarker).

Group comparison was conducted in SPSS 25.0 (SPSS, inc., Beijing, China), and linear regression and linear mixed models were performed in R software version 4.02 (https://www.r-project.org/).

To rule out confounding by WMH and lacune, and to investigate the location specificity of PVS, their relationships (WMH, the presence of lacune or CS-PVS) with CSF biomarkers and cognitive decline were further explored using a similar statistical approach.

2.9 Data Availability Statement

The data was publicly available on PPMI website (https://www.ppmi-info.org/access-data-specimens/).

3. Results

3.1 Baseline features of the included patients

Four hundred and twenty-three patients with drug-naïve PD were recruited in PPMI cohort. Among these subjects, MRI imaging or T2-weighted imaging was missing in 47 patients, and imaging in another 13 patients was not qualified to rate BG-PVS due to incomplete or nonaxial slices. CSF biomarkers were missing in another 22 patients with PD. Finally, 341 patients with complete baseline PVS and CSF biomarkers were included in the present analysis. The included and excluded patients showed overall similar demographic and behavioral profiles (supplementary table 1).

3.2 Group comparison between patients with lower and higher BG-PVS burdens

Compared with patients with lower BG-PVS burden, patients with more severe BG-PVS were significantly older; had more impaired motor function at baseline; had a higher prevalence of previous cardiovascular disease; had a higher prevalence of lacune presence and more severe WMH at baseline; had a higher risk of cognitive impairment and a greater decline in the MoCA score at the 3-year follow-up despite of similar baseline MoCA scores; and showed lower levels of CSF $A\beta_{42}$, $A\beta_{42}$/tTau,

$A\beta_{42}$/pTau and higher levels of CSF α-syn, tTau and pTau at baseline (**Table 1**).

3.3 Univariable linear regression for cognition at the 3-year follow-up

Using the absolute MoCA score at the 3-year follow-up as the dependent variable, age, baseline MoCA score, MDS-UPDRS III total score, tremor, bradykinesia, and axial subscores, RBDSQ, UPSIT score, CSF $A\beta_{42}$, tTau, pTau, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, putamen asymmetry and BG-PVS were significantly associated with cognition at the 3-year follow-up in PD patients ($P<0.05$).

Using decline in MoCA score as the dependent variable, age, baseline MoCA score, RBDSQ, UPSIT score, axial subscore of MDS-UPDRS III, CSF $A\beta_{42}$, tTau, pTau, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, putamen asymmetry, and BG-PVS were significantly associated with cognitive decline during three years in PD patients ($P<0.05$) (supplementary table 2).

3.4 ***Multivariable linear regression for cognition at the 3-year follow-up***

In multivariable regression models, BG-PVS was significantly associated with MoCA score or change in MoCA score, independent of age, past-history cardiovascular diseases, baseline MoCA score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, putamen asymmetry, WMH Fazekas score, the presence of lacune, and CSF biomarkers. Baseline CSF $A\beta_{42}$, $A\beta_{42}$/tTau and $A\beta_{42}$/pTau were significantly associated with the MoCA score or change in the MoCA score at 3-year follow-up independent of age, past-history cardiovascular diseases, baseline MoCA score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, putamen asymmetry, WMH Fazekas score, the presence of lacune, and BG-PVS. However, baseline CSF tTau and pTau were not significantly associated with either cognitive outcome at year three after adjustment (supplementary table 3).

3.5 ***Interaction between CSF biomarkers and BG-PVS***

There was a significant main effect of BG-PVS and CSF $A\beta_{42}$/tTau, $A\beta_{42}$/pTau and $A\beta_{42}$ as well as interactions between BG-PVS and these CSF biomarkers (**Table 2**), such that patients with higher BG-PVS and lower $A\beta_{42}$/tTau (**Figure 1A**), $A\beta_{42}$/pTau (**Figure 1B**), or $A\beta_{42}$ (**Figure 1C**) showed steeper decline in the MoCA score at the 3-year follow-up. Models containing interaction terms provided a slightly improved fit. As patients with a higher BG-PVS burden had a higher prevalence of cardiovascular disease, we further tested whether the interaction between BG-PVS and CSF biomarkers was confounded by the presence of cardiovascular disease. However, the correlation between CSF biomarkers and cognitive decline was not stratified by the presence of cardiovascular disease (supplementary figure 2).

We further compared CSF biomarkers at each follow-up timepoint between the BG-PVS groups. The results revealed that patients with more severe BG-PVS showed significantly higher levels of all measured CSF biomarkers at baseline, 1-year follow-up, and 2-year follow-up, and the significant difference in tTau and pTau was still observed at year three with corrected P values ($P<0.01$) (supplementary table 4).

3.6 ***Path analysis***

In path analysis, CSF $A\beta_{42}$/tTau was found to mediate the effect of BG-PVS on cognitive decline (total effect [original coefficient] = -0.256, direct effect [corrected coefficient] = -0.208, indirect effect = -0.048) (**Figure 2A**). That is, CSF $A\beta_{42}$/tTau mediated 18.8% (indirect effect/total effect) of the BG-PVS effect on the decrease in MoCA scores during the 3-year follow-up. In path analysis, the correlation of BG-PVS with $A\beta_{42}$/pTau was marginally significant, and that with $A\beta_{42}$ was not significant (**Figure 2B and 2C**).

3.7 ***Additional analysis with WMH and CS-PVS***

To rule out the confounding effect of WMH, lacune and CS-PVS, additional analysis was performed.

No significant association was found among WMH, CSF biomarkers, and cognitive outcome; among the presence of lacune, CSF biomarkers, and cognitive outcome; and among CS-PVS, CSF biomarkers, and cognitive outcome (see supplementary figure 3 and supplementary result).

4. Discussion

This is the first study that examined the relationship among CSF biomarkers, cognitive outcome and PVS visible on MRI in PD. The main finding demonstrated that BG-PVS was independently associated with cognitive decline in patients with PD. In addition, BG-PVS modified the pathologic effect of $A\beta_{42}$/tTau, $A\beta_{42}$/pTau, and $A\beta_{42}$ on cognitive decline in PD. Path analysis confirmed that CSF biomarkers, especially $A\beta_{42}$/tTau, partially mediated the pathologic effect of BG-PVS on cognitive outcomes in PD. These results suggest that the increased visibility of BG-PVS on MRI may reflect more advanced glymphatic dysfunction, resulting in higher levels of toxic CSF proteins, which may in turn accelerate neurodegenerative processes and cognitive decline. It also implies that the glymphatic pathway may serve as a therapeutic target to preserve cognition in neurodegenerative disease.

Our results validated a previous study by Park and colleagues [18], and showed that BG-PVS was associated with 3-year cognitive decline in patients with PD. In addition, the contribution to poor cognitive outcome and the interaction with CSF proteins were specific for PVS located in the basal ganglia but not the centrum semiovale. However, the underlying mechanism for the location specificity remains unclear. Evidence suggests that cerebral arterial pulsation drove CSF-interstitial fluid exchange mediated by the glymphatic pathway [19], and arterial stiffness was associated with a higher BG-PVS burden [20]. It is possible that PVS in the basal ganglia may be more prone to arterial damage and pulsation change during aging. However, we did not test arterial function, such as arterial stiffness and regulation. Future studies will be needed to test this hypothesis. In addition, BG-PVS differs from CS-PVS in structure, as BG-PVS is covered by two leptomeningeal membranes and directly connects CSF [21]. This means that BG-PVS may be more active in eliminating waste from CSF, and the increased visibility of BG-PVS may represent an increased effort in waste clearance. Future studies directly comparing CSF dynamics are needed to investigate the location difference of PVS.

Moreover, the results suggested that PVS visible on MRI may reflect glymphatic dysfunction, impaired efflux of CSF proteins and more advanced neurodegeneration in patients with PD. Previous evidence suggested that patients with PD showed higher volume fraction of PVS, especially for those familial patients with genetic mutation [22]. Previous PPMI data also suggested that PVS in midbrain was associated neurodegenerative imaging marker (DAT deficiency) [23]. These findings support our hypothesis that PVS visible on MRI may be closely linked with neurodegeneration in patients with PD. We found that the level of neurodegenerative CSF proteins ($A\beta_{42}$/tTau) partially mediated the effect of BG-PVS on poor cognitive outcome. Taking that CSF proteins, including Aβ and Tau, are toxic to neurons and glial cells [7] and AD biomarkers are predictive of cognitive decline in PD [1-3], the result implies that BG-PVS may contribute to cognitive decline by elevating toxic CSF proteins in patients with PD.

The glymphatic pathway has drawn much attention in recent years as a novel pathway to exclude neurotoxic proteins and a potential therapeutic target [24]. In patients with superficial sclerosis, PVS was enlarged beneath the affected area where Aβ was deposited in the cortical arterial wall by biopsy, supporting the notion that enlarged PVS is a sign of a blocked drainage pathway by proteins such as Aβ [25]. Ding and colleagues specifically tested the meningeal lymphatic flow in patients with PD using dynamic contrast-enhanced MRI, and proved significant reduction of lymphatic flow as well as notable delay in deep cervical lymph node perfusion in these patients. In addition, the delayed meningeal lymphatic drainage was followed by α-syn pathology in mice model [8, 22]. This study provided direct evidence of impaired glymphatic system in PD and the consequent neurodegeneration (e.g. α-syn pathology). PVS visible on routine MRI may be an alternative way to explore the static glymphatic pathway offline.

In PD patients with higher BG-PVS burden, the CSF $A\beta_{42}$ level was lower compared with patients with mild or none BG-PVS. Hypothetically, reduced efflux as a result glymphatic dysfunction should cause increased CSF protein level. As for $A\beta_{42}$, it is possible that the decreased CSF $A\beta_{42}$ reflected more extensive peptide aggregation and plaque formation in brain tissue. Tau and Aβ have independent as well as synergistic effects on cognition [26]. In our analysis, the interaction between CSF biomarker and BG-PVS was more predominant for $A\beta_{42}$/tTau, and $A\beta_{42}$/pTau, compared with $A\beta_{42}$ alone. It is possible that glymphatic dysfunction blocked CSF toxic proteins, and the interaction between these increased proteins (e.g. Tau- $A\beta_{42}$ interaction) accelerated the aggregation of amyloid, lowering the amounts of $A\beta_{42}$ being tested in CSF.

CSF $A\beta_{42}$, $A\beta_{42}$/tTau, and $A\beta_{42}$/pTau were not specific PD biomarkers. However, concurrent proteinopathies and their synergistic interactions are quite common and may contribute to cognitive decline in patients with PD [27]. There might be concomitant AD pathology playing a role in our findings. Previous studies suggested that PVS in the centrum semiovale and hippocampus was associated with the diagnosis of AD [28, 29], and PVS in the hippocampus was associated with hippocampal atrophy[29]. However, the association between PVS visible on MRI and CSF biomarkers was not statistically significant in cognitively impaired individuals in Neurodegenerative Disorders Early and Reliably (BioFINDER) study [29]. More studies are needed to test the association between

PVS visible on MRI and CSF biomarkers in demented and non-demented populations.

In addition to our initial hypothesis, the factors associated with 3-year cognitive decline were largely consistent with previous 2-year follow-up analysis [16]. More recently, Irwin and colleagues reported that AD-related CSF biomarkers were associated with 3-year cognitive decline in a PPMI cohort [17]. Although finding risk factors associated with cognitive decline was not the main topic of our study, the consistency with previous data suggests that the present data are representative of the whole cohort despite missing BG-PVS data in 59 patients (missing rate = 13.9%).

We acknowledge several limitations. First, this study did not measure the dynamic function of the glymphatic pathway in vivo. Currently, dynamic fluid exchange by the glymphatic pathway has been investigated in vivo by intrathecal injection of the contrast agent in neurological diseases such as idiopathic normal pressure hydrocephalus [6]. These approaches enable tracking uptake and distribution of tracers dynamically, but they are invasive and may not be applicable in patients with PD. Second, although CSF $A\beta_{42}$ and Tau are consistently found to be associated with cognitive decline in PD, they are not PD-specific biomarkers. In addition, the findings of the present study only represent the PD population. Whether proteinaceous waste such as Aβ and Tau drives the increased visibility of PVS on MRI and potentially mediates its toxicity needs to be tested in the AD population and normal aging population.

In conclusion, we found that BG-PVS may be independently associated with cognitive decline in PD, which may be partially mediated by toxic CSF proteins. The increased visibility of BG-PVS on MRI may reflect more advanced glymphatic dysfunction. PVS may serve as a therapeutic target to preserve cognition in PD.

Conflict of interest

None

Acknowledgements

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Figure legends

Figure 1. Correlation between CSF biomarkers and cognitive outcomes stratified by BG-PVS

BG-PVS modified the effect of $A\beta_{42}$/tTau (A), $A\beta_{42}$/pTau (B), $A\beta_{42}$ (C) on cognitive outcome in Parkinson's disease, as high BG-PVS group showed steeper decline in the MoCA score in relation to CSF biomarkers at the 3-year follow-up.

Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid.

Figure 2. Path analysis

CSF $A\beta_{42}$/tTau, but not $A\beta_{42}$/pTau or CSF $A\beta_{42}$ significantly mediated the effect of BG-PVS on cognitive decline in patients with PD.

Abbreviations: BG-PVS, basal-ganglia perivascular space; CSF, cerebrospinal fluid; WMH, white matter hyperintensity.

Supplementary figures:

FIG. S1. Correlation between CSF biomarkers

Abbreviations: CSF, cerebrospinal fluid.

FIG. S2. Correlation between CSF biomarkers and cognitive decline stratified by the presence of cardiovascular disease

The presence of cardiovascular disease did not modify the effect of CSF biomarkers on cognitive decline in patients with PD.

FIG. S3. Path analysis for WMH, lacune, and CS-PVS

CSF biomarkers did not mediate the effect of WMH, the presence of lacune or CS-PVS on cognitive decline in PD.

Table 1. Demographic information between groups stratified by BG-PVS

	PD with low BG-PVS (N = 286)	PD with high BG-PVS (N = 55)	P value
Demographic			
Age (median, IQR, year)	60.7 (53.5–66.6)	71.1 (67.1–74.8)	**<0.001**
Gender (F/M)	100/186	15/40	0.269
Disease profile			
Disease duration (median, IQR, month)	4 (2–7)	6 (3–13)	0.066
MoCA Score (median, IQR)	28 (26–29)	27 (25–29)	0.222
Hoehn-Yahr staging (median, IQR)	2 (1–2)	2 (2–2)	**0.001**
MDS-UPDRS III total (median, IQR)	19 (14–26)	22 (16–27)	**0.024**
Tremor subscore (median, IQR)	5 (2–8)	6 (2–9)	0.117
Bradykinesia subscore (median, IQR)	11 (6–15)	14 (9–19)	**0.008**
Axial subscore (median, IQR)	4 (2–5)	4 (3–7)	**0.008**
Rigidity subscore (median, IQR)	4 (2–6)	5 (3–9)	**0.031**
State Trait Anxiety Score (median, IQR)	94 (89–98)	94 (88–97)	0.500
Geriatric Depression Scale (median, IQR)	5 (5–6)	5 (4–6)	0.280
CSF biomarkers			
CSF α-synuclein (median, IQR, pg/ml)	1351.3 (1029.3–1718.0)	1528.8 (1164.3–2086.0)	**0.016**
CSF $A\beta_{42}$ (median, IQR, pg/mL)	848.6 (615.1–1119.0)	822.2 (627.9–1050.5)	0.860

CSF pTau (median, IQR, pg/mL)	13.0 (10.9–16.7)	15.4 (12.4–21.4)	**0.001**
CSF tTau (median, IQR, pg/mL)	152.6 (124.0–192.6)	186.4 (147.2–237.7)	**<0.001**
CSF $A\beta_{42}$/tTau	5.81 (4.69–6.69)	4.88 (3.71–6.01)	**0.002**
CSF $A\beta_{42}$/pTau	69.4 (57.4–80.3)	61.1 (42.7–75.7)	**0.002**
DAT striatal binding ratios			
Mean caudate uptake (median, IQR)	2.02 (1.67–2.37)	1.88 (1.54–2.21)	0.155
Mean putamen uptake (median, IQR)	1.79 (1.48–2.18)	1.77 (1.34–2.08)	0.270
Caudate asymmetry (median, IQR)	1.19 (1.10–1.31)	1.17 (1.07–1.27)	0.216
Putamen asymmetry (median, IQR)	1.45 (1.19–1.76)	1.39 (1.17–1.73)	0.484
Small vessel disease profile			
WMH Fazekas score (median, IQR)	2 (1–2)	3 (2–4)	**<0.001**
The presence of lacune (N, %)	145 (50.7%)	45 (81.8%)	**<0.001**
Cardiovascular diseases (N, %)	224 (52.1%)	57 (77.0%)	**<0.001**
Cerebrovascular diseases (N, %)[a]	2 (0.5%)	2 (2.7%)	0.195
Genetic profile			
Presence of APOE ε4 allele (N, %)	68 (23.8%)	13 (23.6)	0.982
Cognition at 3-year follow-up			
Change in MoCA score (median, IQR)	0 (-2–1)	-2 (-5–0.25)	**0.004**
Cognitive impairment (N, %)	46 (18.9)	22 (48.9%)	**<0.001**

[a]Correction for continuity was adapted for inadequate event.

Abbreviations: CSF, cerebrospinal fluid; DAT, dopaminergic transporter; IQR, interquartile range; MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Score part III; MoCA, Montreal Cognitive Assessment.

Table 2. Linear mixed model for interactive effect of CSF markers and BG-PVS on cognitive outcomes

	MoCA score at 3-year follow-up				Change in MoCA from baseline to 3-year follow-up			
	Model without interaction		Model with interaction		Model without interaction		Model with interaction	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
Model 1								
Baseline $A\beta_{42}$/tTau	0.385 (0.154–0.617)	**0.001**	1.087 (0.650–1.524)	**<0.001**	0.388 (0.156–0.619)	**0.001**	1.086 (0.649–1.523)	**<0.001**
BG-PVS≥2	REF		REF		REF		REF	
BG-PVS<2	1.302 (0.271–2.334)	**0.014**	6.364 (3.515–9.214)	**<0.001**	1.317 (0.285–2.349)	**0.013**	6.357 (3.507–9.207)	**<0.001**
$A\beta_{42}$/tTau*BG-PVS interaction	/		-0.953 (-1.460–-0.445)	**<0.001**	/		-0.949 (-1.456–-0.441)	**<0.001**
AIC	823.4		811.4		823.2		811.3	
Model 2								
Baseline $A\beta_{42}$/pTau	0.031 (0.011–0.050)	**0.002**	0.095 (0.059–0.131)	**<0.001**	0.031 (0.011–0.050)	**0.002**	0.095 (0.059–0.131)	**<0.001**

BG-PVS≥2	REF		REF		REF		REF	
BG-PVS<2	1.364 (0.282–2.445)	**0.014**	7.040 (4.170–9.909)	**<0.001**	1.387 (0.305–2.468)	**0.013**	7.057 (4.186–9.927)	**<0.001**
$A\beta_{42}$/pTau*BG-PVS interaction	/		-0.088 (-0.130–-0.046)	**<0.001**	/		-0.088 (-0.130–-0.046)	**<0.001**
AIC	782.6		772.5		782.4		772.3	
Model 3								
Baseline $A\beta_{42}$	0.001 (0–0.002)	**0.033**	0.003 (0.001–-0.005)	**0.003**	0.001 (0–0.002)	**0.034**	0.003 (0.001–0.005)	**0.003**
BG-PVS≥2	REF		REF		REF		REF	
BG-PVS<2	1.286 (0.253–2.318)	**0.015**	3.328 (1.224–5.432)	**0.002**	1.299 (0.266–2.331)	**0.014**	3.326 (1.221–5.430)	**0.002**
$A\beta_{42}$*BG-PVS interaction	/		-0.002 (-0.004–0)	**0.029**	/		-0.002 (-0.004–0)	**0.030**
AIC	867.6		874.8		867.9		875.2	

CSF biomarkers ($A\beta_{42}$, $A\beta_{42}$/tTau, $A\beta_{42}$/pTau), BG-PVS and their interaction were fixed effect; age, baseline MoCA score, axial subscore of MDS-UPDRS III, RBDSQ, UPSIT, and putamen asymmetry, WMH Fazekas score, the presence of lacune, past history cardiovascular diseases were set as random effect.; Abbreviations: AIC, Akaike information criterion; BG-PVS, basal ganglia perivascular space; REF, reference.

Figure 1

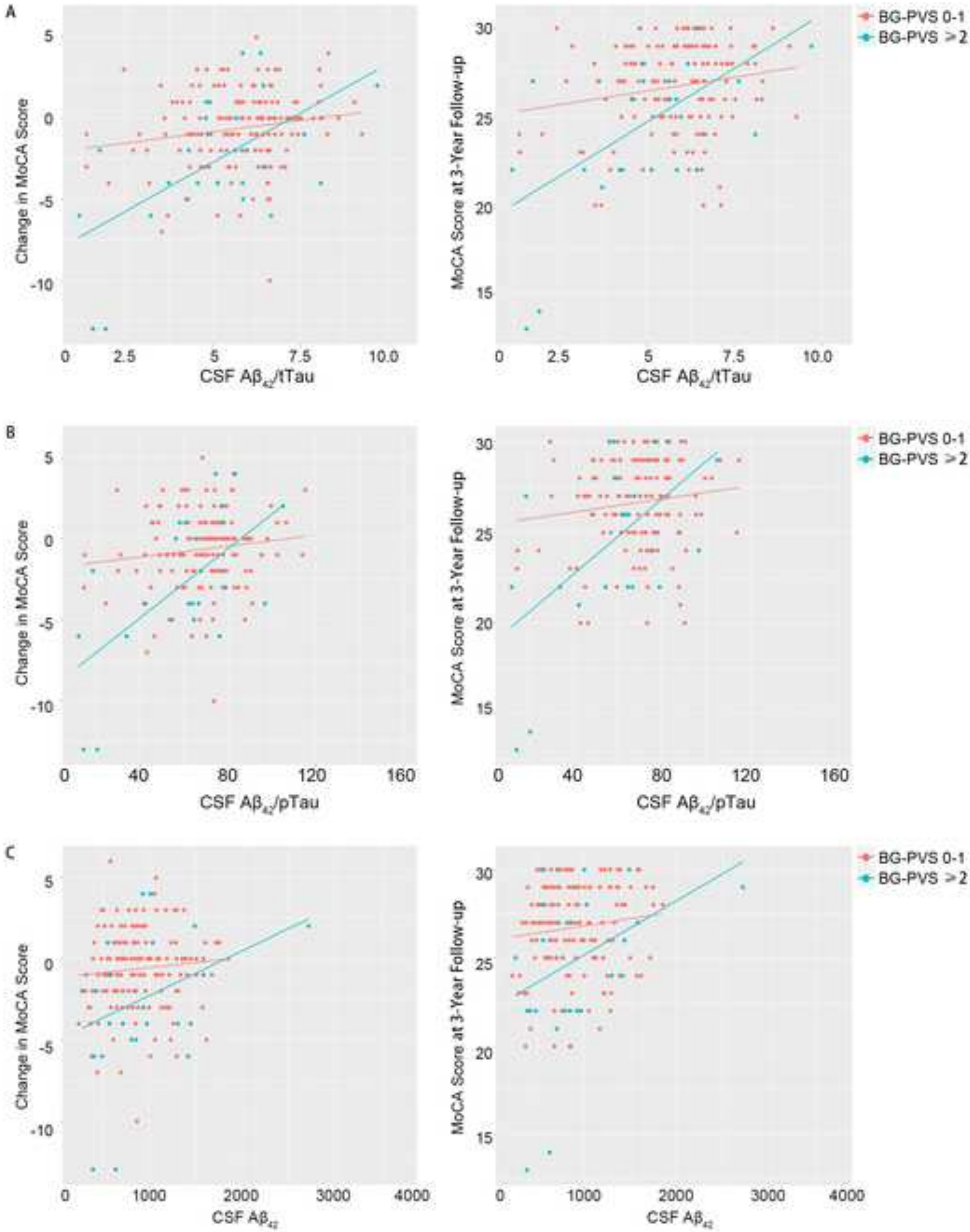
A
Change in MoCA Score
CSF Aβ42/tTau
MoCA Score at 3-Year Follow-up
BG-PVS 0-1
BG-PVS >2
B
CSF Aβ42/pTau
C
CSF Aβ42

Figure 2

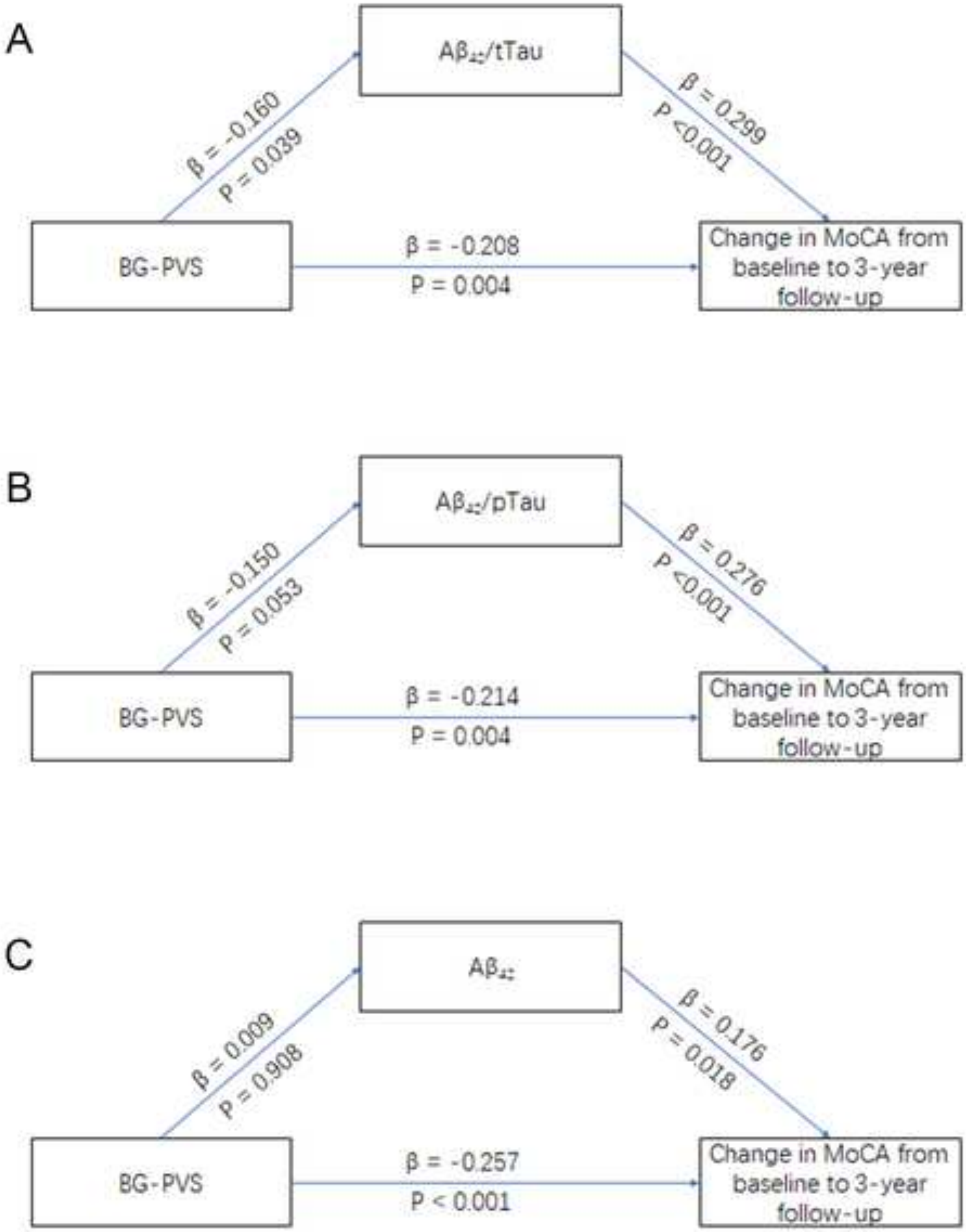
A
Aβ42/tTau
β = -0.160
P = 0.039
β = 0.299
P <0.001
BG-PVS
β = -0.208
P = 0.004
Change in MoCA from baseline to 3-year follow-up
B
Aβ42/pTau
β = -0.150
P = 0.053
β = 0.276
P <0.001
BG-PVS
β = -0.214
P = 0.004
Change in MoCA from baseline to 3-year follow-up
C
Aβ42
β = 0.009
P = 0.908
β = 0.176
P = 0.018
BG-PVS
β = -0.257
P < 0.001
Change in MoCA from baseline to 3-year follow-up

Fig.s1

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