Original Article

# Association between third ventricular width assessed by transcranial sonography and plasma homocysteine in Parkinson's disease with cognitive impairment and their potential to predict conversion to dementia

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**Background:** Cognitive impairment (CI) is a prevalent non-motor symptom in Parkinson's disease (PD) that often leads to disability. This study aimed to explore the association between plasma homocysteine (Hcy) and the width of third ventricle (V3) in PD patients with CI and their potential to predict dementia conversion.

**Methods:** Totals of 118 PD patients with normal cognition (PD-NC), 81 PD patients with mild CI (PD-MCI), 58 PD patients with dementia (PDD), and 35 healthy controls (HCs) were retrospectively recruited. V3 width was measured using transcranial sonography (TCS), plasma Hcy level was quantified using cyclase assay, and cognitive function was analyzed using the Montreal Cognitive Assessment (MoCA).

**Results:** Both V3 width and plasma Hcy concentration were negatively correlated with MoCA scores in PD (r=–0.358, P<0.001; r=–0.187, P=0.013, respectively). Receiver operating characteristic (ROC) analysis suggested that V3 width and Hcy were able to discriminate PDD and PD without dementia [area under the curve (AUC) =0.767 and 0.628, respectively], PD-NC and PD with cognitive decline (AUC =0.735 and 0.657, respectively), and PD-NC and PD-MCI (AUC =0.683 and 0.664, respectively). Following an average follow-up period of 31.04±18.84 months, PD-MCI patients with a V3 width ≥6.55 mm were at a 4.085 times higher risk of developing dementia, whereas PD-NC patients with a V3 width ≥5.75 mm had nearly double the risk of progressing to MCI. However, baseline plasma Hcy levels were unsuitable to predict cognition alternation over time.

**Conclusions:** Plasma Hcy level and V3 width are associated with cognition function severity in PD patients, a V3 width is an independent predictor of MCI-dementia conversion in PD.

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**Keywords:** Parkinson's disease (PD); cognitive impairment (CI); homocysteine (Hcy); third ventricle (V3); transcranial sonography (TCS)

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## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative brain disease characterized by damage to nigrostriatal dopaminergic neurons, representing a severe burden to human health (1). In China, with its large and increasingly aging population, there has been an 89.7% increase in the age-standardized incidence and a 167.8% rise in age-standardized prevalence of PD during 1990–2021 (2). Cognitive impairment (CI), which encompasses mild CI (MCI) and dementia, is a highly prevalent and debilitating nonmotor symptom affecting approximately 15–30% of PD patients (3). The incidence of dementia in individuals with PD is 2.5–6 times higher than in age-matched healthy controls (HCs) (4). Moreover, it is estimated that about 50% of PD patients with normal cognition (PD-NC) will develop CI within 6 years (5), and all newly diagnosed MCI cases progress to dementia within 5 years (5). However, current treatments for PD patients with dementia (PDD) such as oral medications (donepezil and rivastigmine), cognitive training, transcranial direct current stimulation, and repetitive transcranial magnetic stimulation combined with virtual reality have yielded less than satisfactory results (6). CI not only significantly impacts functionality and quality of life but also reduces life expectancy and increases mortality (7), placing a considerable toll on patients, families, and the public healthcare system. In 2020, the *Lancet* Commission suggested that over 40% of dementia cases worldwide could potentially be prevented or delayed, particularly in low- and middle-income countries (8). Therefore, it is crucial for researchers and physicians to identify and predict future dementia in PD patients, considering the variability in timing, characteristics, and pace of cognitive decline within this population.

Neuroimaging is imperative for identifying CI by utilizing positron emission tomography (PET) to assess impaired cholinergic synapses, amyloid, and tau, as well as applying structural magnetic resonance imaging (MRI) to distinguish enlarged vascular gaps and white matter hyperintensity (9,10). These two modalities are time-consuming and costly, and PET induces radiation hazards to the patient. Recent studies have suggested that measuring the width of the third ventricle (V3) using transcranial sonography (TCS) can indirectly indicate cognitive function reproducibly and reliably (11-13). A cross-sectional study verified a correlation between V3 width and CI in PD patients, as well as its' ability to differentiate PDD from those without (12). A longitudinal study further investigated the predictive value of V3 enlargement in cognitive decline after a median follow-up of 21.5 months in 80 PD-NC (11). However, it remains uncertain whether V3 width can serve as a reliable biomarker for predicting the conversion to dementia in the PD population.

Elevated homocysteine (Hcy) levels resulting from L-dopa treatment, along with potential environmental risk factors such as inadequate vitamin B12 (VitB12) or folate, significantly increase the risk of brain atrophy in PD, especially in older adults and those with PDD. Hcy concentration has been found to be associated with cognitive dysfunction in both community dwellings and established PD patients (14), as well as V3 width (15). However, there is currently a lack of longitudinal research specifying predictive potential of Hcy levels in cognitive conversion in PD, as well as investigating the interaction between Hcy levels and V3 width in cognitive progression. Therefore, this study aimed to examine the association between plasma Hcy levels and V3 width assessed by TCS, and to explore their utility in identifying CI and predicting dementia conversion in patients with PD. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1736/rc).

## Methods

### *Participants and controls*

This retrospective study enrolled 257 PD patients [median age, 65 years (range, 26–84 years), 148 males] and 35 age- and sex-matched HC with normal cognition. The sample

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size was determined based on a previous study (11) and the calculation formula for diagnostic experiments: $n = [Z^2_{1-\alpha}/2 \times Sen \times (1 - Sen)]/(L^2 \times P)$. Since the prevalence of PD was approximately normally distributed, a two-sided test level of 0.05 was used with $Z^2_{1-\alpha}/2$ set at 1.96. The diagnostic sensitivity (Sen) of TCS for PD, as reported in the literature (16), was 0.79. The permissible error (L) was set as 0.1, and the prevalence (P) of PD in the Department of Dyskinesia of our research center was estimated to be about 20–25%. Thus, the sample size in the PD group was estimated to be between 130 and 160. To minimize the impact of potential missing values, 257 PD patients who met the inclusion criteria were included from January 2018 to December 2020. All PD participants met the criteria set by the UK Parkinson's Disease Society Brain Bank (17) or the Consensus Statement of the International Parkinson and Movement Disorder Society (MDS) in 2020 (18).

Individuals were excluded if they had Parkinson syndrome caused by cerebrovascular disease, craniocerebral tumors, trauma, or medications, hydrocephalus, insufficient clinical history, ambiguous V3 results of TCS examination for insufficient temporal bone window, implanted deep brain stimulation (DBS) electrodes, stem cell therapy, pallidotomy, CI occurring before the onset of PD, or PD combined with Alzheimer's disease (AD). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Beijing Tiantan Hospital (No. KYSQ 2019-039-01). Each participant provided informed consent.

### *Clinical and neuropsychological assessment*

Age, gender, disease duration, body mass index (BMI), and education level were collected from all participants. Each PD individual underwent a comprehensive set of neurological examinations, including the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), Hoehn and Yahr (H-Y) staging, Montreal Cognitive Assessment (MoCA), and Mini-Mental State Examination (MMSE). The MoCA and MMSE were utilized to evaluate the global cognitive condition of the participants. The study categorized PD patients into three subgroups based on their cognitive status: 118 PD-NC (MoCA score ≥26), 81 PD patients with MCI (PD-MCI; MoCA score ≥20 and <26), and 58 PDD (MoCA score <20 and MMSE score <26), following the MDS level II criteria for CI in PD and dementia criteria in China (19-21). Notably, to investigate alternation in cognition, two subgroups of patients with PD-NC (n=41) and PD-MCI (n=72) were clinically followed up for an average duration of 31.04±18.84 months.

All neuropsychological evaluations were conducted by two neurologists (L.Z.Y. and H.Y.M.) with over 5 years of experience managing patients with movement disorders. In cases where a consistent diagnosis could not be reached, a senior expert (X.M.W.) with over 10 years of experience in treating patients with movement disorders would make the diagnosis.

### *TCS examination*

One sonographer (F.X.L.), with at least 5 years of expertise in neuroimaging, performed the ultrasound examination. The V3 width was measured by two experienced sonographers (F.N. and S.L.) with over 10 years of experience in neuroimaging, who were unaware of the patient's clinical diagnosis. The protocol of TCS examination was consistent with our previous study (22). Canon Aplio i900 ultrasound equipment (Canon, Tochigi, Japan), along with the I6SX1 phased array probe operating at a frequency range of 2.0–3.0 MHz, was used for scanning. Scanning setting details included depth at 14–16 cm, dynamic range at 45–55 dB, and adjustment of brightness and gain compensation as needed. In summary, the patient was positioned supine with the temporal window fully exposed. The probe was placed near the temporal window on one side, and parallel to the canthus line. Then, the probe was gradually tilted at an angle of 10–15° towards the head to display the thalamic plane, from which the V3 can be displayed. The V3 is characterized by two parallel hyperechoic lines located between the thalamus on both sides, positioned anteriorly to the pineal gland. For accuracy and reproducibility, the width of V3 was measured from the inner layer of the hyperechogenic ependyma on one side to the inner layer on the other side, as previously described (11) (*Figure 1*). The measurement was repeated three times to obtain an average value. Interclass correlation coefficient (ICC) was utilized to test interobserver agreement for V3 width calculation.

### *Laboratory measurements*

A fasting venous blood sample of 5 mL was collected in the morning, and the serum was immediately centrifuged, kept at –80 ℃, and analyzed using an immunoturbidimetric assay. Ferritin, folate, and VitB12 levels were measured using a chemiluminescent assay (e601; Roche, Basel,

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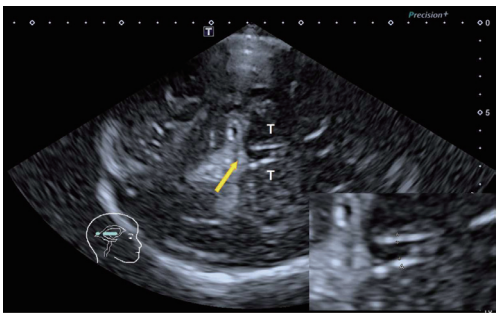


**Figure 1** TCS image depicting the scanning planes at the thalamic level in a patient with PD. TCS image showing the V3 between the hyperechoic lines can be clearly visualized, and the yellow arrow points to the pineal gland, which is easily visible on TCS due to its high echogenicity. PD, Parkinson's disease; T, thalamus; TCS, transcranial sonography; V3, third ventricle.

Switzerland), and Hcy levels were tested by a cyclase assay (Roche AU5800) electrochemiluminescence immunoassay analyzer.

### *Statistical analysis*

The measurement data were presented as mean ± standard deviation or median [interquartile range (IQR)], whereas the discrete variables were expressed as n (%). Differences between groups were compared using one-way analysis of variance (ANOVA) followed by Bonferroni's corrected post hoc comparisons or unpaired independent *t*-test (for continuous variables with normal distributions), the Kruskal-Wallis test followed by Dunn's corrected post hoc comparisons or Mann-Whitney *U* test (for non-parametric data), or the Chi-squared test (for categorical variables). Spearman correlation analysis and partial correlation analysis were performed to assess the associations between V3 width, plasma Hcy levels, and demographic information. The diagnostic efficacy of biomarkers was compared by utilizing receiver operating characteristic (ROC) curve analysis and identifying the cut-off values derived from maximizing the Youden index. The Cox regression model was utilized to explore the relationship between initial V3 width, plasma Hcy levels, and cognition function in the follow-up data. A P value <0.05 was considered statistically significant. All statistical analyses were performed using the software SPSS 25.0 (IBM Corp., Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA).

## Results

The baseline demographic and clinical characteristics of the participants are shown in *Table 1*, whereas the general information about global PD patients can be found in Table S1. The patient selection flow diagram is available in Figure S1. The ICC for V3 width assessment was 0.90 (range, 0.88–0.93) between the two raters, indicating a high level of interobserver agreement. There were no statistical differences in age, gender, BMI, education level, plasma folate, VitB12, or ferritin across the four groups (all P>0.05); however, there were significant differences in plasma Hcy (adjusted P<0.05) and V3 width (adjusted P<0.001). Compared with the PD-NC and PD-MCI groups, the PDD group had a longer disease duration (all adjusted P<0.05), a greater H-Y stage distribution, and a higher UPDRS-III score (all adjusted P<0.001) (*Figure 2A*,*2B*). Additionally, after stratifying the study population by age 60 years, the differences in V3 width among the four groups remained statistically significant (*Table 1*).

Although the gender distribution was obviously different in plasma Hcy and ferritin, it had no significant differences in other variables (Table S2). Spearman correlation analysis indicated that age and disease duration of all PD participants were significantly correlated with the V3 width, H-Y stage, UPDRS-III score, and MoCA score, and disease duration was also significantly correlated with plasma Hcy level in all participants (Table S3). We included age and disease duration as covariates in the relevant comparative analysis for these reasons.

After adjusting for age and disease duration, the results of Spearman partial correlation analysis showed that plasma Hcy was positively correlated with UPDRS-III, whereas V3 width was positively correlated with H-Y stage and UPDRS-III score. Furthermore, significant correlations between V3 width and MoCA (r=–0.358, P<0.001), plasma Hcy and MoCA (r=–0.187, P=0.013), and V3 width and plasma Hcy (r=0.140, P=0.026) were observed (*Figure 2C*, Table S4).

ROC curve analysis was utilized to examine the discriminating performance of circulating Hcy and V3 width in cognition dysfunction in PD patients. The results suggested that V3 width yielded a reliable differential diagnosis between PDD and PD without dementia (including both PD-NC and PD-MCI), PD-NC and PD with cognitive decline (including both PD-MCI and PDD), as well as PD-MCI and PD-NC. The area under

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**Table 1** Baseline demographic and clinical data of the participants

| Parameters | HC (n=35) | PD-NC (n=118) | PD-MCI (n=81) | PDD (n=58) | P value |
|---|---|---|---|---|---|
| Age (years) | 67 [43, 81] | 63 [37, 83][a] | 67 [26, 84] | 68 [34, 83][b] | 0.009[§] |
| >60 | 4.56±1.33 | 5.23±1.30[g] | 5.72±1.27[a,g] | 6.74±1.56[c,d,f] | <0.001[†] |
| ≤60 | 5.14±0.79 | 4.46±1.10 | 5.01±1.33 | 7.00±2.45[a,d,f] | <0.001[†] |
| Gender (male) | 21 (60.0) | 70 (59.3) | 47 (58.0) | 31 (53.4) | 0.889[‡] |
| BMI (kg/m$^2$) | 24.92±3.01 | 24.21±3.06 | 24.49±3.29 | 23.59±3.60 | 0.224[†] |
| Disease duration (years) | – | 5 [0.2, 18] | 5 [0.5, 20] | 7 [2.0, 25][b,f] | 0.001[§] |
| Education level (years) | 9 [0, 20] | 12 [0, 21] | 9[0, 21] | 9 [0, 20][¶] | 0.099[§] |
| H-Y stage | – | 2.5 [1, 5] | 3 [1, 5] | 3 [1, 5][d,e] | <0.001[§] |
| UPDRS-III | – | 30 [9, 85] | 37 [9, 85] | 53 [16, 89][d,e] | <0.001[§] |
| MoCA | 28 [26, 30] | 27 [26, 30] | 21 [8, 27][c,d] | 12 [3, 22][c,d,f] | <0.001[§] |
| MMSE | 28.97±0.66 | 29.01±1.07 | 25.88±2.49[c,d] | 18.41±3.54[c,d,e] | <0.001[†] |
| Hcy (μmol/L) | 12.84±5.08 | 14.56±5.38[¶] | 17.75±10.70[a,b] | 18.87±8.47[a,b] | <0.001[†] |
| Folate (ng/mL) | 8.49±4.01 | 8.19±4.48[¶] | 8.69±5.83[¶] | 7.48±5.32 | 0.557[†] |
| VitB12 (pg/mL) | 439.34±197.47 | 428.27±268.79[¶] | 493.31±353.27[¶] | 450.16±390.41 | 0.551[†] |
| Ferritin (ng/mL) | 156.22±94.30 | 123.73±110.82 | 147.81±130.49[¶] | 130.72±105.89 | 0.330[†] |
| V3 width (mm) | 4.67±1.25 | 4.92±1.28 | 5.57±1.36[a,b] | 6.80±1.79[c,d,e] | <0.001[†] |

Data are presented as mean ± standard deviation, median [IQR], or n (%). [†], one-way ANOVA followed by Bonferroni's post-hoc correction for multiple comparisons. [‡], $\chi^2$ test. [§], Kruskal-Wallis test with Dunn's post-hoc test. [¶], missing values: education year: PDD 1; Hcy: PD-NC 1; folate: PD-NC 1, PD-MCI 1; VitB12: PD-NC 1, PD-MCI 1. [a], P<0.05 *vs.* HCs. [b], P<0.05 *vs.* PD-NC. [c], P<0.001 *vs.* HCs. [d], P<0.001 *vs.* PD-NC. [e], P<0.001 *vs.* PD-MCI. [f], P<0.05 *vs.* PD-MCI. [g], inter-groups comparison P<0.05. ANOVA, analysis of variance; BMI, body mass index; HC, healthy control; H-Y, Hoehn and Yahr; Hcy, homocysteine; IQR, interquartile range; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; PDD, Parkinson's disease with dementia; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; V3, third ventricle; VitB12, vitamin B12.

the curve (AUC) values for V3 width were 0.767 [95% confidence interval (CI): 0.694–0.839], 0.735 (95% CI: 0.674–0.796), and 0.683 (95% CI: 0.606–0.761) for the respective comparisons. In contrast, the AUC values for plasma Hcy were 0.628 (95% CI: 0.543–0.712), 0.657 (95% CI: 0.590–0.723), and 0.664 (95% CI: 0.585–0.743) for the same comparisons (*Figure 2D-2F*).

To investigate the predictive value of V3 width for the conversion from normal cognition to MCI conversion and from MCI to dementia in PD, a total of 41 PD-NC patients and 72 PD-MCI patients were followed over an average period of 31.04±18.84 months. The PD-NC group cases were followed for a mean duration of 32.41±22.29 months, whereas those with MCI were followed up for 30.25±16.68 months. In terms of PD-NC patients, 23 (56.1%) progressed to MCI and 1 (2.4%) developed PDD. Some 23.6% of PD-MCI patients progressed to PDD. Tables S5-S7 provide detailed demographic and clinical information for PD patients with follow-up and those without, as well as information on cognitive stability and progression during the follow-up period. PD-MCI patients with a V3 width ≥6.55 mm at baseline had a significantly higher risk for developing PDD compared to those with a V3 width <6.55 mm (hazard ratio =4.085; 95% CI: 1.922–8.682; P<0.001; Sen 77.8%; specificity 90.7%). Furthermore, the PD-NC patients had a nearly two-fold increased risk of converting to MCI if their baseline V3 width was ≥5.75 mm, with a Sen of 62.5% and specificity of 100% (*Table 2*). Notably, baseline plasma Hcy level was not a significant predictor of cognitive changes during long-term follow-up according to the Cox regression analysis.

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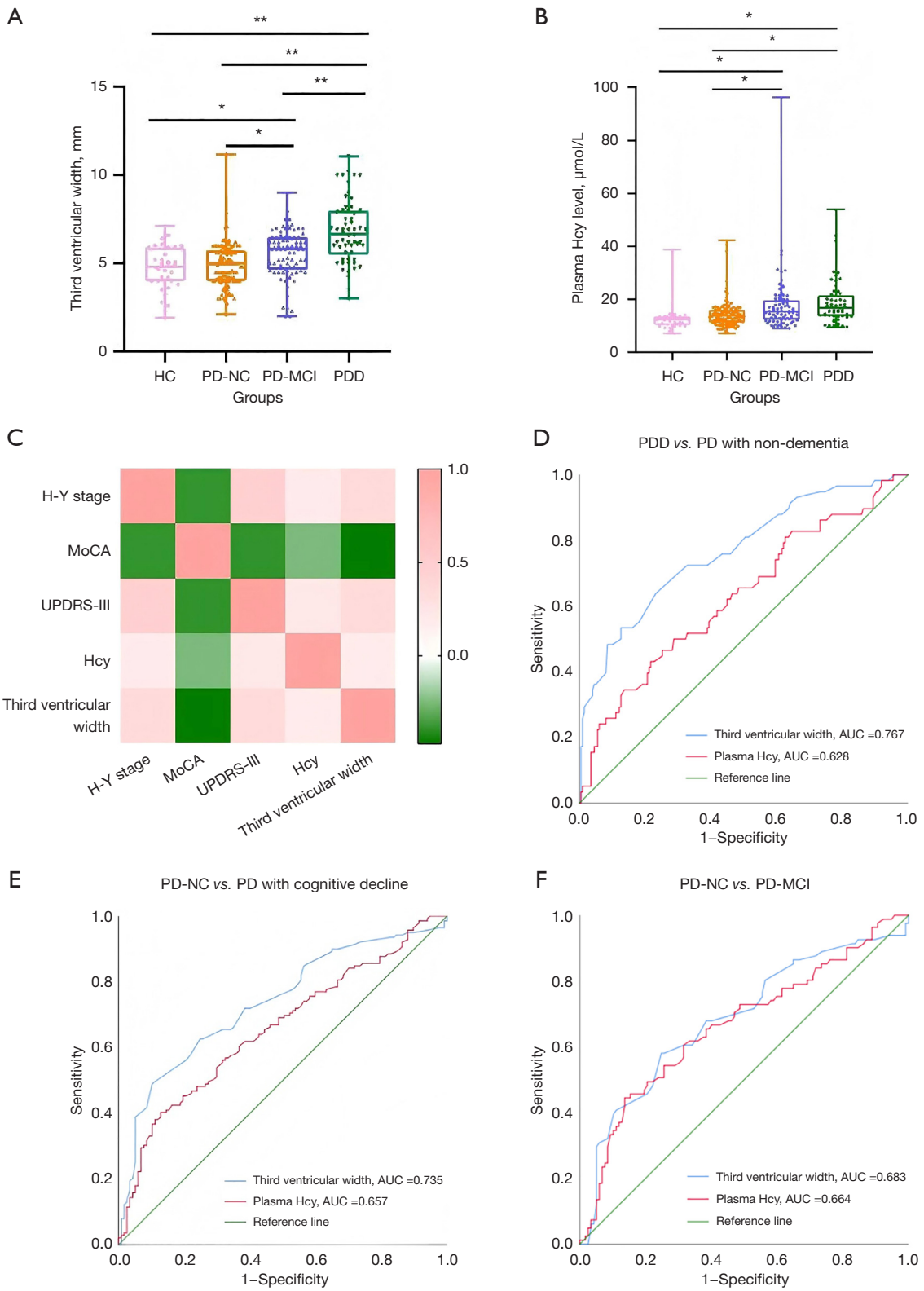


**Figure 2** Diagnostic performance of V3 width and plasma Hcy. (A,B) The V3 width (A) and plasma Hcy levels (B) in HC (n=35) and patients with PD-NC (n=118), PD-MCI (n=81), and PDD (n=58). Groups were compared by one-way ANOVA followed by Bonferroni's post-hoc

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correction. Boxes show the mean ± standard deviation, and whiskers are the minimum and maximum. Dots are single values. *, P<0.05; **, P<0.001. (C) Spearman partial correlation analysis of H-Y stage, UPDRS-III, MoCA score, Hcy, and the V3 width after adjusting age and disease duration. The correlation coefficient r is shown in the heat map. Line color represents the direction of correlation: red (positive), green (negative), the deeper the color, the stronger the correlation. (D-F) ROC curve analysis exhibited the efficiency of V3 width and plasma Hcy in distinguishing between PDD and those without dementia (D), PD-NC and those with cognitive decline (E), and PD-NC and PD-MCI (F). ANOVA, analysis of variance; AUC, area under the curve; HC, healthy control; H-Y, Hoehn and Yahr; Hcy, homocysteine; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; PDD, Parkinson's disease with dementia; ROC, receiver operating characteristic; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; V3, third ventricle.

**Table 2** Cox regression analysis of V3 width as a predictor of cognitive progression in PD patients

| Followed-up PD patients with differ V3 width | Cognition decline | Cognition stable | HR (95% CI) | P value | Sen (%) | Specificity (%) |
|---|---|---|---|---|---|---|
| PD-MCI | | | 4.085 (1.922, 8.682) | <0.001 | 77.8 | 90.7 |
| V3 width ≥6.55 mm | 14 | 5 | | | | |
| V3 width <6.55 mm | 4 | 49 | | | | |
| PD-NC | | | 1.709 (1.084, 2.694) | 0.021 | 62.5 | 100.0 |
| V3 width ≥5.75 mm | 15 | 0 | | | | |
| V3 width <5.75 mm | 9 | 17 | | | | |

CI, confidence interval; HR, hazard ratio; PD, Parkinson's disease; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; Sen, sensitivity; V3, third ventricle.

## Discussion

The main findings of our study revealed that PDD and PD-MCI exhibited higher levels of plasma Hcy concentration and a wider V3 width compared to PD-NC patients and the HC group. Both plasma Hcy levels and V3 width showed a significant negative correlation with MoCA scores in PD patients. Additionally, there was a slight positive correlation between plasma Hcy levels and V3 width in PD patients. The measurement of V3 width using TCS has potential to distinguish between PDD, PD-MCI, and PD-NC. It may also serve as an independent neuroimaging biomarker for predicting cognitive decline and the progression from MCI to dementia in PD.

The degree of parkinsonism was associated with the extent of atrophy in the V3 region, as evaluated through structural MRI. This study observed a negative relationship between the width of V3, assessed by TCS, and the MoCA score, which indicates the severity of cognitive dysfunction in PD. TCS is a cost-effective and reliable alternative to MRI for evaluating the width of V3 in patients with metallic foreign objects or those experiencing claustrophobia. A previous study determined that the thresholds for V3 width measured by TCS, indicating the likelihood of diagnosing PDD, were 6.0 mm for individuals under the age of 70 years and 7.5 mm for those over the age of 70 years in the German population (12). Another study conducted in Central China concluded that a V3 width of 4.75 mm has moderate ability to diagnose PD patients with CI with a Sen of 62.7% and a specificity of 75.6% (11). Our ongoing research in North China has identified an optimal cutoff of 5.75 mm for PD-MCI and 6.55 mm for PDD. These variations in cutoff values may be attributed to differences in age, gender, and disease duration, which were identified as distinct risk predictors for cognitive decline in PD (8,23,24). The V3 width measured by TCS can offer valuable insights into the natural aging process and brain atrophy in dementia. Consistent with previous studies (11,12), a positive correlation between age and V3 width was observed. Other factors such as geographic and ethnic differences in the research population, as well as screening tests used for cognitive function assessment (e.g., MMSE and MoCA), could potentially account for the observed

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variations in threshold values. Although TCS has limitations in assessing overall brain atrophy due to its restricted resolution, V3 width remains an easily recognizable structure with a discrimination rate of up to 96%, even in cases with a suboptimal temporal bone window (12).

The pathomorphological correlations of cognitive deficits in PD is heterogeneous, with current knowledge of the pathogenesis of cognitive dysfunction in PD primarily based on influential studies by Braak and colleagues (25,26). They proposed a pattern of Lewy pathology spreading from the rostral to caudal areas of the brain, involving the alpha-synuclein. However, one third of cases in earlier stage 3 of PD show dementia even in the absence of Lewy bodies in the cortex (27). Growing evidence has demonstrated deficits in the cholinergic, dopaminergic, and noradrenergic systems in various regions (which can be detected using molecular imaging techniques), including the lateral geniculate nucleus, hippocampus, caudate nucleus, cingulum, and lateral cortical territories, all of which play a role in driving CI across different domains (28). When the supply of cerebral blood flow is insufficient, both intracranial perfusion and cerebral blood volume are reduced, which further disrupts neurovascular coupling and leads to cognitive decline (29). Despite this complexity, it has been suggested that the widening of V3 width may be an independent risk factor for cognitive progression in PD, regardless of the underlying pathological diversity of CI (12).

Cerebrospinal fluid and plasma levels of β-amyloid and neurofilament light are biological markers of cognitive function in neurodegenerative diseases (30,31). However, some patients may find it uncomfortable to undergo a lumbar puncture to obtain a cerebrospinal fluid sample, and plasma concentrations of these two indicators are not routinely available. Instead, recent studies suggest that elevated plasma Hcy, a marker that can be easily measured in daily tests, is correlated with cognitive deficits in various central nervous system disorders and neurodegenerative diseases (32-34). Possible mechanisms involve Hcy promoting oxidative stress, increasing the release of inflammatory factors such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), and mediating neuronal apoptosis through energy consumption and DNA damage, resulting in death of neuronal cells and brain atrophy (35). It is worth nothing that although Hcy levels are strongly correlated with folate and VitB12, which are coenzymes for methionine and Hcy metabolism, no significant differences were observed in folate and VitB12 levels among the four groups studied. This lack of difference may be due to the routine use of dopamine therapy in patients with PD, which causes an increase in circulating Hcy concentration (36).

Spearman correlation analysis demonstrated a significant relationship among age, disease duration, V3 width, and Hcy level. After adjusting for age and disease duration as covariates, Spearman's partial correlation analysis further supported the connection between V3 width and Hcy concentration in PD, consistent with previous studies by Fu *et al.* and Sapkota *et al.* (15,37). As mentioned before, elevated Hcy levels affect brain volume through a variety of mechanisms, ultimately influencing cognitive function. The dilation of V3 width is associated with cerebral atrophy and enlargement of the periventricular space, providing insight into the positive correlation observed between V3 width and plasma Hcy concentration. In addition to the enlargement of V3, research has shown that increased Hcy levels in PD were associated with cognitive performance and structural damage, such as frontal cortical thinning, and microstructural damage in both frontal and posterior-cortical regions (38). Notably, patients with postural instability gait difficulty phenotype of PD typically exhibit significant cognitive dysfunction and elevated Hcy levels (39). However, the correlation between V3 enlargement and PD subtypes warrants further investigation.

To further investigate the predictive power of baseline V3 width and Hcy level on cognition progression in PD, a follow-up was conducted on 113 patients. The results of the Cox regression model showed that the initial width of V3 significantly predicted the transition from normal cognition to MCI, and from MCI to dementia. PD-MCI patients with a V3 width greater than 6.55 mm had a four-fold increased risk of developing dementia compared to those with a V3 width lower than 6.55 mm. Setting a cutoff value of 5.75 mm for the V3 width resulted in lower Sen (62.5% *vs.* 77.7%) but higher specificity (100% *vs.* 90.6%) in detecting cognitive decline. These findings align with the research conducted by Gao *et al.* (11). However, our study found that the initial Hcy level was not a reliable predictor of cognition shifts. Unlike Sleeman *et al.*'s study (40), which focused on newly diagnosed PD-NC, our study included patients at various disease stages and receiving treatment, potentially impacting Hcy levels. This approach reflects the clinical reality, as not all patients presenting to the clinic have newly identified and untreated PD. Although both V3 dilation and high Hcy levels are linked to cognitive decline in PD, V3 and age are positively correlated with cerebral atrophy, which is challenging to reverse once present. An enlarged V3 exhibits reduced responsiveness to medication.

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In contrast, as mentioned before, Hcy levels are influenced by several factors, such as dietary deficiencies in VitB12 and folate, as well as daily oral administration of L-dopa in patients with PD. Consequently, plasma Hcy levels may fluctuate. This variability may help to explain why the V3 is more useful in predicting dementia transition whereas plasma Hcy levels are not.

Some limitations need to be addressed. Firstly, in the present study, we applied MoCA and MMSE to evaluate the cognitive status of the participants. However, we did not delve into a detailed analysis of the correlation between the certain domains of MoCA/MMSE and V3 width and Hcy levels. Consequently, we were unable to conduct a comprehensive analysis of the specific cognitive aspects affected by V3 dilation and elevated Hcy concentration. Secondly, due to the irregularity in follow-up durations and the limited observation period of some individuals (which may not have been sufficient to adequately track cognitive changes in PD patients), we were unable to carry out a Kaplan-Meier curve analysis based on cognitive ability or consistently monitor changes in V3 widths and Hcy levels over time. However, these areas could be a direction for future research. Additionally, due to limitations in sample size and the necessity for subsequent follow-up, we did not conduct age stratification when evaluating the predictive performance of V3 width on CI. Given that the V3 width varies between younger and older individuals, it is essential to stratify the V3 width by age in future studies to more accurately assess its predictive value for PDD across different age groups. Moreover, it is important to highlight that there was a significant overlap between the groups, and although the ROC curves showed moderate accuracy, the Spearman correlations, although statistically different, were quite modest (ranging from 0.1 to 0.4). Larger cohort studies in the future, incorporation of wider range of TCS parameters and biomarkers, along with the combination of various subtypes of PD, will enhance our exploration of their impact on CI in PD.

## Conclusions

The study revealed a correlation between V3 dilation measured through TCS, elevated plasma Hcy levels, and the severity of cognitive decline in PD patients. The baseline width of the V3 was identified as a promising neuroimaging biomarker with the potential to predict cognition dysfunction and the conversion from mild MCI to dementia in PD.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Beijing Tiantan Hospital (No. KYSQ 2019-039-01). Each participant provided informed consent.

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## References

1. Ben-Shlomo Y, Darweesh S, Llibre-Guerra J, Marras C, San Luciano M, Tanner C. The epidemiology of Parkinson's disease. Lancet 2024;403:283-92.
2. Xu T, Dong W, Liu J, Yin P, Wang Z, Zhang L, Zhou M. Disease burden of Parkinson's disease in China and its provinces from 1990 to 2021: findings from the global burden of disease study 2021. Lancet Reg Health West Pac

2024;46:101078.
3. Carceles-Cordon M, Weintraub D, Chen-Plotkin AS. Cognitive heterogeneity in Parkinson's disease: A mechanistic view. Neuron 2023;111:1531-46.
4. Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, Weintraub D. Parkinson disease-associated cognitive impairment. Nat Rev Dis Primers 2021;7:47.
5. Pigott K, Rick J, Xie SX, Hurtig H, Chen-Plotkin A, Duda JE, Morley JF, Chahine LM, Dahodwala N, Akhtar RS, Siderowf A, Trojanowski JQ, Weintraub D. Longitudinal study of normal cognition in Parkinson disease. Neurology 2015;85:1276-82.
6. Foltynie T, Bruno V, Fox S, Kühn AA, Lindop F, Lees AJ. Medical, surgical, and physical treatments for Parkinson's disease. Lancet 2024;403:305-24.
7. Daelman B, Van Bulck L, Luyckx K, Kovacs AH, Van De Bruaene A, Ladouceur M, et al. Frailty and Cognitive Function in Middle-Aged and Older Adults With Congenital Heart Disease. J Am Coll Cardiol 2024;83:1149-59.
8. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413-46.
9. Groot C, Smith R, Collij LE, Mastenbroek SE, Stomrud E, Binette AP, Leuzy A, Palmqvist S, Mattsson-Carlgren N, Strandberg O, Cho H, Lyoo CH, Frisoni GB, Peretti DE, Garibotto V, La Joie R, Soleimani-Meigooni DN, Rabinovici G, Ossenkoppele R, Hansson O. Tau Positron Emission Tomography for Predicting Dementia in Individuals With Mild Cognitive Impairment. JAMA Neurol 2024;81:845-56.
10. van der Heide FCT, Steens ILM, Limmen B, Mokhtar S, van Boxtel MPJ, Schram MT, Köhler S, Kroon AA, van der Kallen CJH, Dagnelie PC, van Dongen MCJM, Eussen SJPM, Berendschot TTJM, Webers CAB, van Greevenbroek MMJ, Koster A, van Sloten TT, Jansen JFA, Backes WH, Stehouwer CDA. Thinner inner retinal layers are associated with lower cognitive performance, lower brain volume, and altered white matter network structure-The Maastricht Study. Alzheimers Dement 2024;20:316-29.
11. Gao HL, Qu Y, Chen SC, Yang QM, Li JY, Tao AY, Mao ZJ, Xue Z. Third ventricular width by transcranial sonography is associated with cognitive impairment in Parkinson's disease. CNS Neurosci Ther 2024;30:e14360.
12. Behnke S, Pilotto A, Liepelt-Scarfone I, Yilmaz R, Pausch C, Dieterich S, Bürmann J, Spiegel J, Dillmann U, Unger M, Posner I, Berg D. Third ventricular width assessed by transcranial ultrasound correlates with cognitive performance in Parkinson's disease. Parkinsonism Relat Disord 2019;66:68-73.
13. Lu Y, Dong W, Xue X, Sun J, Yan J, Wei X, Chang L, Zhao L, Luo B, Qiu C, Zhang W. The severity assessment of Parkinson's disease based on plasma inflammatory factors and third ventricle width by transcranial sonography. CNS Neurosci Ther 2024;30:e14670.
14. Weekman EM, Johnson SN, Rogers CB, Sudduth TL, Xie K, Qiao Q, Fardo DW, Bottiglieri T, Wilcock DM. Atorvastatin rescues hyperhomocysteinemia-induced cognitive deficits and neuroinflammatory gene changes. J Neuroinflammation 2023;20:199.
15. Fu XY, Zhang YC, Ding CW, Yang M, Song X, Wang CS, Chen XF, Zhang Y, Sheng YJ, Mao P, Mao CJ, Liu CF. Association between homocysteine and third ventricle dilatation, mesencephalic area atrophy in Parkinson's disease with cognitive impairment. J Clin Neurosci 2021;90:273-8.
16. Heim B, Peball M, Hammermeister J, Djamshidian A, Krismer F, Seppi K. Differentiating Parkinson's Disease from Essential Tremor Using Transcranial Sonography: A Systematic Review and Meta-Analysis. J Parkinsons Dis 2022;12:1115-23.
17. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591-601.
18. Khalil H, Chahine LM, Siddiqui J, Salari M, El-Jaafary S, Aldaajani Z, Abu Al-Melh M, Mohammad TM, Abu Snineh M, Syed NA, Bhatt M, Habib MA, Habahbeh M, Tabbal SD, Jeon B, Bajwa JA. Parkinson's Disease in the Middle East, North Africa, and South Asia: Consensus from the International Parkinson and Movement Disorder Society Task Force for the Middle East. J Parkinsons Dis 2020;10:729-41.
19. Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, Mollenhauer B, Adler CH, Marder K, Williams-Gray CH, Aarsland D, Kulisevsky J, Rodriguez-Oroz MC, Burn DJ, Barker RA, Emre M. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27:349-56.
20. Skorvanek M, Goldman JG, Jahanshahi M, Marras C, Rektorova I, Schmand B, van Duijn E, Goetz CG, Weintraub D, Stebbins GT, Martinez-Martin P; members

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of the MDS Rating Scales Review Committee. Global scales for cognitive screening in Parkinson's disease: Critique and recommendations. Mov Disord 2018;33:208-18.
21. Chinese Society of Parkinson's Disease and Movement Disorders; Parkinson's Disease and Movement Disorder Section of Neurologist Branch of Chinese Medical Doctor Association; Chinese Society of Neuropsychology and Behavioral Neurolog. The diagnostic criteria and treatment guideline for Parkinson's disease dementia (second version). Chinese Journal of Neurology 2021;54:762-71.
22. Hou C, Yang F, Li S, Ma HY, Li FX, Zhang W, He W. A nomogram based on neuron-specific enolase and substantia nigra hyperechogenicity for identifying cognitive impairment in Parkinson's disease. Quant Imaging Med Surg 2024;14:3581-92.
23. Boccalini C, Carli G, Pilotto A, Padovani A, Perani D. Gender differences in dopaminergic system dysfunction in de novo Parkinson's disease clinical subtypes. Neurobiol Dis 2022;167:105668.
24. Liu G, Locascio JJ, Corvol JC, Boot B, Liao Z, Page K, et al. Prediction of cognition in Parkinson's disease with a clinical-genetic score: a longitudinal analysis of nine cohorts. Lancet Neurol 2017;16:620-9.
25. Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson's disease. Parkinsonism Relat Disord 2010;16:79-84.
26. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197-211.
27. Braak H, Rüb U, Jansen Steur EN, Del Tredici K, de Vos RA. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 2005;64:1404-10.
28. van der Zee S, Müller MLTM, Kanel P, van Laar T, Bohnen NI. Cholinergic Denervation Patterns Across Cognitive Domains in Parkinson's Disease. Mov Disord 2021;36:642-50.
29. Zhu WM, Neuhaus A, Beard DJ, Sutherland BA, DeLuca GC. Neurovascular coupling mechanisms in health and neurovascular uncoupling in Alzheimer's disease. Brain 2022;145:2276-92.
30. Lerche S, Wurster I, Röben B, Zimmermann M, Machetanz G, Wiethoff S, Dehnert M, Rietschel L, Riebenbauer B, Deuschle C, Stransky E, Lieplt-Scarfone I, Gasser T, Brockmann K. CSF NFL in a Longitudinally Assessed PD Cohort: Age Effects and Cognitive Trajectories. Mov Disord 2020;35:1138-44.
31. Lin J, Ou R, Li C, Hou Y, Zhang L, Wei Q, Pang D, Liu K, Jiang Q, Yang T, Xiao Y, Zhao B, Chen X, Song W, Yang J, Wu Y, Shang H. Plasma glial fibrillary acidic protein as a biomarker of disease progression in Parkinson's disease: a prospective cohort study. BMC Med 2023;21:420.
32. Christine CW, Auinger P, Joslin A, Yelpaala Y, Green R; Parkinson Study Group-DATATOP Investigators. Vitamin B12 and Homocysteine Levels Predict Different Outcomes in Early Parkinson's Disease. Mov Disord 2018;33:762-70.
33. Ding L, Liu Y, Meng X, Jiang Y, Lin J, Cheng S, Xu Z, Zhao X, Li H, Wang Y, Li Z. Biomarker and genomic analyses reveal molecular signatures of non-cardioembolic ischemic stroke. Signal Transduct Target Ther 2023;8:222.
34. Hooshmand B, Appold F, Fissler P, Perneczky R, Otto M, Tumani H, Kivipelto M, von Arnim CAF. Markers of Vitamin B12 Status in Relation to Cerebrospinal Fluid Biomarkers of Alzheimer's Disease and Cognitive Performance. Ann Neurol 2023;94:223-31.
35. Zhou L. Homocysteine and Parkinson's disease. CNS Neurosci Ther 2024;30:e14420.
36. Boelens Keun JT, Arnoldussen IA, Vriend C, van de Rest O. Dietary Approaches to Improve Efficacy and Control Side Effects of Levodopa Therapy in Parkinson's Disease: A Systematic Review. Adv Nutr 2021;12:2265-87.
37. Sapkota S, Gee M, Sabino J, Emery D, Camicioli R. Association of homocysteine with ventricular dilatation and brain atrophy in Parkinson's disease. Mov Disord 2014;29:368-74.
38. Sampedro F, Martínez-Horta S, Horta-Barba A, Grothe MJ, Labrador-Espinosa MA, Jesús S, et al. Increased homocysteine levels correlate with cortical structural damage in Parkinson's disease. J Neurol Sci 2022;434:120148.
39. You Z, Ma S, Xu H, Wu Z, You Z. Comorbidity of white matter lesions in parkinson's disease: a study on risk factors and phenotypic differences. Neurol Sci 2025;46:175-83.
40. Sleeman I, Lawson RA, Yarnall AJ, Duncan GW, Johnston F, Khoo TK, Burn DJ. Urate and Homocysteine: Predicting Motor and Cognitive Changes in Newly Diagnosed Parkinson's Disease. J Parkinsons Dis 2019;9:351-9.

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