Neurological Sciences (2019) 40:1855–1863
https://doi.org/10.1007/s10072-019-03906-3

ORIGINAL ARTICLE

Association of homocysteine, folate, and white matter hyperintensities in Parkinson's patients with different motor phenotypes

Yuan Shen[1,2] · Zhi-feng Dong[3] · Ping-Lei Pan[2] · Gang Xu[5] · Jun-Ying Huang[1] · Chun-Feng Liu[1,4]

Received: 19 November 2018 / Accepted: 15 April 2019 / Published online: 4 May 2019

Abstract

Objective To investigate the association of homocysteine (Hcy), folate, and white matter hyperintensities in Parkinson's disease (PD) with different motor phenotypes.

Methods Of the PD patients, 176 were included. Based on the Unified Parkinson's Disease Rating Scale, the PD patients were classified into postural instability gait disorder (PIGD) and non-PIGD phenotypes. According to the Fazekas score, patients were divided into the none/mild white matter hyperintensity (WMH) group and the moderate/severe WMH group. The relationship of Hcy, folate, and white matter hyperintensities (WMHs), and the motor phenotype of PD were analyzed.

Results PD-PIGD patients had higher proportion of moderate/severe WMHs, Hcy levels, and lower folate levels than PD-non-PIGD patients (p all ≤ 0.001). In the subgroup analysis, patients with both PD-PIGD and moderate/severe WMHs had the highest Hcy and lowest folate levels compared with others. Binary logistic regression analysis showed that age, folate, and Hcy were independent risk factors for WMHs. In an a priori-determined stratified analysis, after adjustment for confounding factors, the odds ratio of WMHs was 8.01 (95% CI 2.700–23.767, p trend = 0.001) in the patients with Hcy levels in the highest quintile compared with the lowest quintile and 16.81 (95% CI 4.74–59.65, p trend < 0.001) in the patients with folate levels in the lowest quintile compared with the highest quintile.

Conclusions Our data showed a close association between WMHs and Hcy, folate especially in PD-PIGD patients. It can be speculated that higher Hcy and lower folate probably played important roles in the development of WMHs and motor heterogeneity in PD.

Keywords Parkinson's disease · Homocysteine · Folate · White matter hyperintensities · Motor phenotype

Introduction

White matter hyperintensities (WMHs) are frequent comorbidities in Parkinson's disease (PD). Combined pathological findings of PD and white matter and/or basal ganglia lesions may determine a different clinical course and prognosis than those with isolated PD [1]. Previous studies showed that WMHs correlated with axial motor impairment and were associated with cognition in PD patients [2, 3]. However, the underlying biological mechanism of WMHs in PD has yet to be elucidated. Recently, the vascular hypothesis has been greatly developed, proposing a key role for neurovascular changes in neuronal dysfunction and loss [4–8]. Evidence has accumulated that vascular factors play an important role in the etiology of WMHs, including hypertension [9, 10], diabetes mellitus [11], obesity [12, 13], and smoking [14]. However, the risk factors of WMHs in PD patients have not been made clear.

✉ Chun-Feng Liu
liuchunfeng@suda.edu.cn

1 Department of Neurology and Suzhou Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China

2 Department of Neurology, Affiliated Yancheng Hospital, School of Medicine, Southeast University, Yancheng, China

3 Department of Cardiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

4 Department of Neurology Institute of Neuroscience, The Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Suzhou 215004, China

5 Department of Medical Imaging, Affiliated Yancheng Hospital, School of Medicine, Southeast University, Yancheng, China

Homocysteine (Hcy) is a sulfur-containing amino acid formed by interconversion of methionine and cysteine. Hcy has a variety of neurotoxic effects in the pathogenesis of a variety of neurodegenerative diseases, including dementia and PD [15, 16]. In recent years, many studies have investigated the associations between Hcy and PD and shown that patients with PD have increased levels of Hcy in comparison with age-matched healthy controls [17, 18]. Hyperhomocysteinemia (HHcy) may lead to dopaminergic cell death through neurotoxicity in PD patients [17, 19, 20]. Therefore, regulation of Hcy metabolism may reduce the risk of PD by reducing plasma Hcy. Folate and vitamin B_{12} are significant determinants of Hcy levels. A previous study on a cohort of psychiatric patients showed that HHcy and low folate levels were associated with white matter hyperintensities [21].

However, to date, the existing evidence on the relevance of WMHs and Hcy in PD is limited [2, 22]. The study on the relevance of WMHs and folate in PD has not been reported. In the present study, we aimed to investigate the relationships between plasma Hcy and folate and WMHs, as well as the association between the presence of WMHs and motor phenotype in PD. We hypothesized that HHcy and low folate levels can accelerate the progression of PD by affecting white matter lesions. By discovering the risk factors for PD with white matter lesions, this work may lead to a new intervention strategy. We also hypothesized that HHcy and low folate levels might affect the disparity between the postural instability gait disorder (PIGD) and tremor dominant phenotypes by aggravating WMHs.

Methods

Subjects

PD patients were recruited from the Center of Parkinsonism and Movement Disorders in our hospital from September 2013 to July 2017. The study was approved by our hospital's ethical committee. All participants provided written informed consent to participate.

Inclusion criteria

The diagnosis of PD was based on the UK Parkinson's Disease Society Brain Bank clinical diagnosis criteria [23]. All patients had positive levodopa response during at least 1-year follow-up visits, and none met diagnostic criteria for vascular parkinsonism [24].

Exclusion criteria

Patients were excluded if they had any of the following: (1) secondary parkinsonian syndrome; (2) solid malignancy or hematological disorders; (3) acute or chronic infections or hepatic or renal diseases; (4) current vitamin supplementation; (5) history of cerebrovascular disease.

Demographics, clinical characteristics, laboratory tests, and imaging assessment

We recorded the following information for all patients: gender, age, body mass index (BMI), PD duration, medication type, dose, frequency, time, and duration of use, and vascular risk factors such as arterial hypertension, ischemic heart disease, atrial fibrillation, diabetes mellitus, hyperlipidemia, cigarette smoking, and alcohol consumption. Medication dosages were converted to levodopa dosage equivalents (LDE) using the unified formula [25]: (regular LD dose) + (LD CR dose × 0.75) + (LD × 0.33 if entacapone) + (pramipexole dose × 100) + (ropinirole dose × 20) + (rotigotine dose × 30) + (pergolide dose × 1) + (bromocriptine dose × 10) + (selegiline dose × 10) + (rasagiline dose × 100) + (amantadine dose × 1).

Disease severity was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr (H&Y) stage. All rating scales were performed by two neurologists in movement disorders. According to the classification for clinical phenotypes (the ratio of mean tremor score/mean PIGD score) by Jankovic et al. [26], ratio scores ≥ 1.5 identified subjects with the TD subtype, ratio scores ≤ 1.0 the PIGD subtype, and 1.0 < ratio scores < 1.5 the indeterminate subtype. Due to a relative small sample number of the indeterminate subtype in our sample, the TD and indeterminate groups were combined to form a single non-PIGD group for subsequent analyses.

For all patients, blood samples were taken from a peripheral vein in the morning after a 12-h fasting period and were tested for fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, creatinine, uric acid, cystatin C (CysC), homocysteine, folate, and vitamin B_{12}.

All MRIs were performed with a Philips Intera 1.5 T (Philips Medical Systems, the Netherlands). Axial T2-weighted images, complemented with coronal fluid-attenuated inversion recovery (FLAIR), were used for measuring white matter lesion (WML) volume. For cerebral MRI, the extent of deep WMHs (DWM) and periventricular WMHs (PVH) was scored using the Fazekas score (0 = absent, 1 = punctate foci, 2 = beginning confluence areas, 3 = large confluent areas). All scoring was performed consistently by the same neuroradiologist. The severity was graded as none (0), mild (1), moderate (2), or a marked decrease in the attenuation of white matter (3). Participants were divided into two groups according to their WMH scores: group 0, none to mild (WMH score 0–1), and group 1, moderate to severe (WMH score ≥ 2).

Statistical analysis

SPSS for Windows, version 23.0 (IBM Corporation, New York, USA), was used for statistical analysis. Continuous variables are

Table 1 The comparison of demographics and basic disease characteristics between PD-non-PIGD and PD-PIGD

Characteristics	All ($n = 176$)	PD-non-PIGD ($n = 40$)	PD-PIGD ($n = 136$)	p
Male sex, n (%)	64 (36.4)	20 (50.0)	44 (32.4)	0.041
Age	63.78 ± 10.25	66.00 ± 9.59	63.13 ± 10.38	0.120
BMI	22.83 ± 3.41	23.43 ± 3.98	22.66 ± 3.22	0.229
PD duration	4.00 (2.00, 6.00)	3.00 (1.25, 4.75)	4.00 (2.00, 6.00)	0.129
Hoehn and Yahr stage	2.00 (1.50, 2.50)	2.00 (1.25, 2.50)	2.00 (1.50, 2.50)	0.311
UPDRS III	22.00 (16.00, 30.00)	22.00 (13.00, 23.75)	22.00 (17.00, 32.00)	0.007
LDE	300.00 (0, 487.50)	106.25 (0, 300.00)	300.00 (0, 500.00)	0.014
Vascular risk factors				
Hypertension (%)	56 (31.8)	20 (50.0)	36 (26.5)	0.005
Diabetes (%)	16 (9.1)	4 (10.0)	12 (8.8)	0.820
Smoking (current) (%)	22 (12.5)	4 (10.0)	18 (13.2)	0.587
Alcohol consumption (%)	12 (6.8)	2 (5.0)	10 (7.4)	1.000
UA (μmol/L)	294.13 ± 73.69	290.05 ± 93.55	295.32 ± 67.12	0.741
LDL (mmol/L)	2.65 ± 0.75	2.64 ± 0.65	2.66 ± 0.78	0.865
TC (mmol/L)	4.60 ± 0.92	4.69 ± 0.87	4.57 ± 0.94	0.484
GLU (mmol/L)	5.07 (4.67, 5.39)	5.07 (4.76, 5.44)	5.07 (4.62, 5.37)	0.209
CysC (mg/L)	0.98 (0.86, 1.16)	0.97 (0.81, 1.12)	0.99 (0.89, 1.16)	0.175
Vitamin B_{12} (pg/mL)	384.00 (292.25, 420.00)	385.00 (332.23, 438.25)	384.00 (278.97, 420.00)	0.591
Folate (ng/mL)	9.16 ± 4.30	12.14 ± 5.08	8.28 ± 3.62	< 0.001
Hcy (μmol/L)	15.01 ± 7.35	12.30 ± 4.73	15.81 ± 7.79	0.001
WMHs (moderate/severe) (%)	102 (58.0)	24 (44.4)	78 (63.9)	0.016

Values are presented as mean ± standard deviation or median (interquartile range), and categorical variables are presented as percentage (%)

BMI body mass index, *PD* Parkinson's disease, *UPDRS* Unified Parkinson's Disease Rating Scale, *PIGD* postural instability gait disorder, *LDE* levodopa dosage equivalents, *UA* uric acid, *LDL* low-density lipoprotein, *TC* total cholesterol, *GLU* glucose, *CysC* cystatin C, *Hcy* homocysteine

presented as the mean ± standard deviation or median (interquartile range), and categorical variables are presented as percentages (%). The chi-square test was used for categorical data. The normally distributed variables were compared using an independent t test and analyses of variance. And the continuous non-normally distributed variables were compared using a Mann-Whitney U test. Spearman's correlation coefficients were computed to examine the relationships between clinical manifestations and WMHs. Binary logistic regression was used for the multivariate analysis of the baseline characteristics as risk factors for WMHs. Binary logistic regression was used to estimate the odds ratio (OR) of WMHs by quantiles of Hcy and folate levels, stratified by four categories. A test for a linear trend was conducted with the use of quantiles of the Hcy and folate level variables as

Table 2 The comparison of WMH data between PD-non-PIGD and PD-PIGD patients

WMH	All patients ($n = 176$)	PD-non-PIGD ($n = 40$)	PD-PIGD ($n = 136$)	p value
Moderate to severe WMH (score ≥ 2, %)	102 (58.0)	14 (35.0)	88 (64.7)	0.001
Moderate to severe PVH (≥ 2, %)	70 (39.8)	20 (50.0)	50 (36.8)	0.133
Moderate to severe DWM (≥ 2, %)	28 (15.9)	6 (15.0)	22 (16.2)	0.858
WMH score	2.00 (1.00, 3.00)	1.00 (0, 3.00)	2.00 (1.00, 3.00)	0.039
PVH score	1.00 (1.00, 2.00)	1.50 (0, 2.00)	1.00 (1.00, 2.00)	0.893
DWM score	1.00 (0, 1.00)	0.50 (0, 1.00)	1.00 (0, 1.00)	0.028

Values are presented as median (interquartile range), and categorical variables are presented as percentage (%)

PD Parkinson's disease, *PIGD* postural instability gait disorder, *WMHs* white matter hyperintensities, *PVHs* periventricular hyperintensities, *DWMs* deep white matter hyperintensities

Table 3 Binary logistic regression model examining predictors of motor subtypes (PIGD and non-PIGD subtypes)

WMHs	Unadjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)[a]	*p* value
Moderate to severe WMH (score ≥ 2, %)	3.405 (1.626–7.128)	0.001	3.799 (1.771–8.150)	0.001
Moderate to severe PVH (score ≥ 2, %)	0.580 (0.286–1.184)	0.135	0.508 (0.243–1.060)	0.070
Moderate to severe DWM (score ≥ 2, %)	1.094 (0.410–2.915)	0.858	1.164 (0.431–3.147)	0.765
WMH score	1.304 (0.989–1.718)	0.060	1.301 (0.989–1.712)	0.060
PVH score	1.122 (0.733–1.716)	0.596	1.050 (0.683–1.614)	0.824
DWM score	1.773 (1.027–3.060)	0.040	1.833 (1.059–3.172)	0.030

WMHs white matter hyperintensities, *PVHs* periventricular hyperintensities, *DWMs* deep white matter hyperintensities, *OR* odds ratio, *CI* confidence interval

[a] Adjusted for gender

continuous variables by assigning the median values of the quintiles to the variables. A $p < 0.05$ and 95% confidence intervals of OR (logistic regression) that excluded 1.0 were considered statistically significant.

Results

In total, 176 patients with PD were included in this study. Basic demographics and clinical characteristics of all the subjects and the PIGD and non-PIGD phenotypes are summarized in Table 1. Of all the participants, 40 patients (22.7%) were classified as the non-PIGD phenotype, and 136 patients (77.3%) were classified as the PIGD phenotype.

Comparisons of demographic data and motor characteristics between the PD-non-PIGD and PD-PIGD phenotypes are summarized in Table 1. PD-PIGD patients had a lower proportion of male gender ($p = 0.041$), higher UPDRS III score ($p = 0.007$), and higher LDE ($p = 0.014$) than PD-non-PIGD patients. The PD-PIGD patients had higher Hcy plasma levels than PD-non-PIGD patients ($p = 0.001$) and lower folate levels than PD-non-PIGD patients ($p < 0.001$). The PD-PIGD patients had lower proportion of hypertension ($p = 0.005$) than the PD-non-PIGD patients.

MRI findings

WMHs based on the Fazekas score are summarized in Table 2. As indicated, the DWM score was higher in PD-PIGD patients than in PD-non-PIGD patients ($p = 0.028$), and the proportion of moderate to severe WMHs was higher in PD-PIGD patients than that in PD-non-PIGD patients ($p = 0.001$). After adjusting for gender, the WMHs were still the independent risk factor of motor phenotype (Table 3).

In the entire PD cohort, those with moderate to severe WMHs had significantly higher Hcy levels and lower folate levels than those with none to mild WMHs (Figs. 1 and 2). In the subgroup analysis, patients with both PD-PIGD and moderate/severe WMHs had the highest Hcy and lowest folate levels compared with others (Fig. 3).

In the entire PD cohort, Spearman's correlation analyses of all variables showed that the WMHs correlated with age ($r = 0.387$, $p < 0.001$), smoking ($r = -0.165$, $p = 0.028$), CysC ($r = 0.298$, $p < 0.001$), folate ($r = -0.309$, $p < 0.001$), and

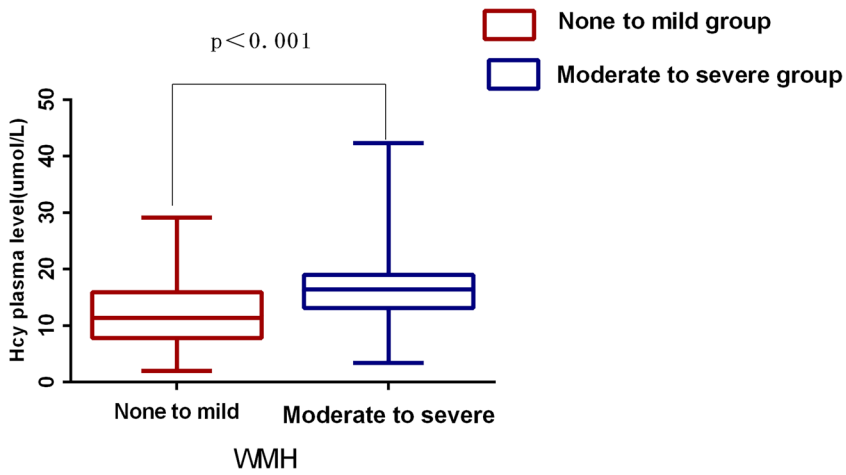

Fig. 1 Comparison of Hcy levels in PD patients with none to mild vs. moderate to severe WMHs

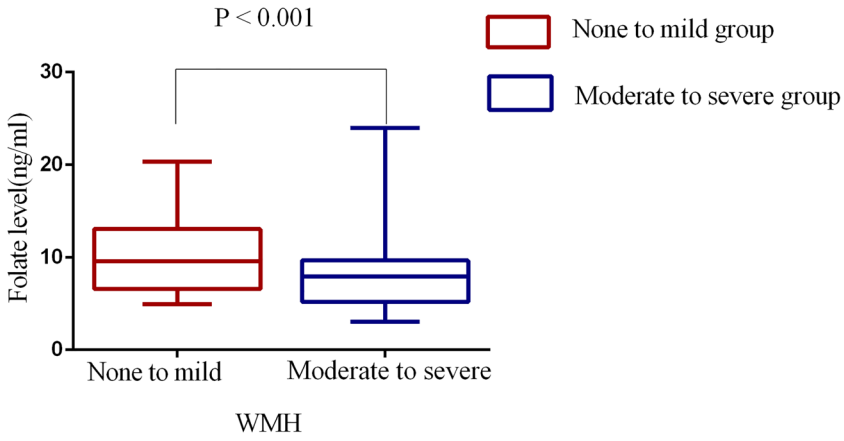

Fig. 2 Comparison of folate levels in PD with none to mild vs. moderate to severe WMHs

Hcy ($r = 0.355$, $p < 0.001$). No significant correlations were found among the remaining variables (Table 4). Binary logistic regression analysis showed that age (OR [95% CI] = 1.103 [1.058–1.151], $p < 0.001$), folate level (OR [95% CI] = 0.826 [0.751–0.908], $p < 0.001$), and Hcy level (OR [95% CI] = 1.124 [1.036–1.195], $p < 0.001$) were independent risk factors for WMHs (Table 5).

The association of Hcy, folate, and risk of WMHs is presented in Table 6. In an a priori-determined stratified analysis, we found that there were significant positive associations between Hcy and WMHs. A higher Hcy level was associated with a significantly higher risk of moderate to severe WMHs when adjusting for age (OR = 5.228, 95% CI 2.035–13.428, p trend = 0.001) and after further adjustment for folate and vitamin B_{12} (OR = 8.085, 95% CI 2.823–23.153, p trend < 0.001). After further adjustment for CysC, hypertension, diabetes, and alcohol consumption, the association of Hcy with WMHs was not attenuated (OR = 8.011, 95% CI 2.700–23.767, p trend = 0.001) in the patients with levels of Hcy in the highest quintile compared with the lowest. There were significant associations between low folate and WMHs. A lower folate level was associated with a significantly higher risk of moderate to severe WMHs when adjusting for age (OR = 8.14, 95% CI 2.95–22.41, p trend < 0.001) and after further adjustment for Hcy and vitamin B_{12} (OR = 18.81, 95% CI 5.42–65.27, p trend < 0.001). After further adjustment for CysC, hypertension, diabetes, and alcohol consumption, the association of folate with WMHs was not attenuated (OR = 16.81, 95% CI 4.74–59.65, p trend < 0.001) in the patients with levels of folate in the lowest quintile compared with the highest.

Discussion

In this study, we found in PD patients that moderate to severe WMHs were related to higher Hcy and lower folate levels in the entire PD sample independent of age, CysC, hypertension, low-density lipoprotein cholesterol, and vitamin B_{12}. Moreover, a greater proportion of cases with moderate to severe WMHs were identified in PD-PIGD than in PD-non-PIGD patients.

WMHs are frequently viewed as a marker of small-vessel disease related to vascular risk factors. WMHs appear to contribute to the development of gait disorders in PD [2, 3]. Based on this background, we believe that it is important to understand which factors may contribute to the development of WMHs in these patients, as such insights may provide new therapeutic targets. Many risk factors, such as hypertension, diabetes, smoking, and advanced age, are classic risk factors for WMHs. In addition to these risk factors, some studies have shown that Hcy was associated with WMHs [27, 28]. This is

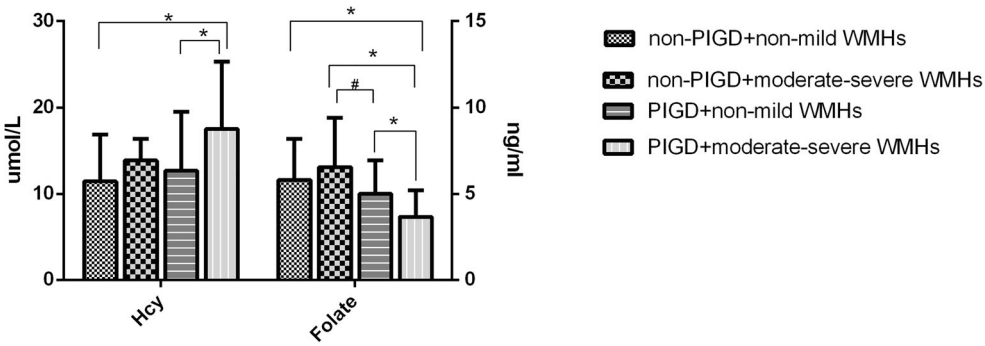

Fig. 3 Comparison of Hcy levels and folate levels in different motor phenotypes and WMHs. #< 0.01, *< 0.001

Table 4 Correlation analysis of clinical characteristics and WMHs

Clinical characteristics and laboratory parameters	WMHs	
	r	*P*
Gender	− 0.070	0.359
Age	0.387	< 0.001
PD duration	0.045	0.566
Hoehn and Yahr stage	− 0.121	0.111
UPDRS III	− 0.145	0.055
LDE	0.123	0.105
Hypertension	0.137	0.070
Diabetes	0.029	0.701
Smoking	− 0.165	0.028
Drinking	− 0.044	0.566
UA	− 0.039	0.608
LDL	0.129	0.089
TC	0.035	0.649
GLU	− 0.079	0.298
CysC	0.298	< 0.001
Vitamin B_{12}	− 0.102	0.176
Folate	− 0.309	< 0.001
Hcy	0.355	< 0.001

WMHs white matter hyperintensities, *PD* Parkinson's disease, *UPDRS* Unified Parkinson's Disease Rating Scale, *PIGD* postural instability gait disorder, *LDE* levodopa dosage equivalents, *UA* uric acid, *LDL* low-density lipoprotein, *TC* total cholesterol, *GLU* glucose, *CysC* cystatin C, *Hcy* homocysteine

consistent with our research findings. In our study, there was a positive correlation between Hcy and WMHs. A higher Hcy level was associated with a significantly higher risk of moderate to severe WMHs even after adjusting for age, folate, vitamin B_{12}, CysC, hypertension, diabetes, and alcohol consumption in the patients with levels of Hcy in the highest quintile compared with the lowest. In this context, it appears interesting to us that this study showed an association between folate and WMHs, independent of homocysteine. Previous studies in a psychiatric cohort found that folate was associated with white matter lesions [21]. However, thus far, no study has investigated the correlation between folate and white matter lesions in PD patients. Previous studies have shown that low folate levels promoted the progression of PD. Folate deprivation makes dopaminergic neurons more sensitive to damage and death, which plays an important role in the pathogenesis of PD [29]. In animal models of parkinsonism, supplementation with folic acid could provide a neuroprotective effect by reducing oxidative stress. The neuroprotective effect of folic acid is not mediated by lowering plasma Hcy [30]. Our study showed that low folate levels were a risk factor of white matter lesions independent of homocysteine in PD patients. Since no patients were clinically deficient in folate in our study group, it may be necessary to rethink the cutoff value of folate that is considered a functionally significant micronutrient deficiency in PD patients. However, other traditional risk factors for vascular diseases, such as hypertension, diabetes, smoking, and alcohol consumption, were not associated with WMHs in PD patients in our study. This may suggest that homocysteine and folate do not affect white matter lesions based on vascular sclerosis but exert effects on white matter alterations through other potential mechanisms, such as increased oxidative stress [15, 16] and increased rate of accumulation of amyloid [31, 32].

Previous studies on WMHs and motor impairment have been inconsistent. Some studies support that WMHs aggravate motor symptoms in PD patients [1, 33, 34], while others have shown that WMHs have no effect on postural instability and gait [35, 36]. In our study, PD-PIGD patients had higher DWM scores and a higher proportion of moderate to severe WMHs than PD-non-PIGD patients. As PIGD and non-PIGD groups were not matched for gender ratio in the demographic data, an important question is whether comorbid moderate/severe WMHs in PD reflect effects of gender. So we used PD-PIGD and PD-non-PIGD subtypes as dependent variable and WMHs as independent variable to carry out binary logistic regression, and after adjusting for gender, as categorical variable, the WMHs were still the independent risk factor of motor phenotype.

Recent studies have supported the relation between motor symptoms and the architecture of the neural network in PD patients [37]. Comorbid WMHs may disconnect local neuronal networks or long association fibers linking distant cortical areas that are important for performing movements with postural control systems [38, 39]. Subcortical WMHs disrupt short corticocortical connections, whereas periventricular WMHs may lead to damage within regions containing coordination of multiple and distinct cortical areas [40]. According

Table 5 Binary logistic regression model examining predictors of WMHs

Variable	Beta coefficient	Standard error	Wald	*p* value	OR	95% CI
Hcy	0.116	0.031	13.704	< 0.001	1.124	1.056–1.195
Folate	− 0.191	0.048	15.588	< 0.001	0.826	0.751–0.908
Age	0.098	0.021	21.325	< 0.001	1.103	1.058–1.151

WMHs white matter hyperintensities, *OR* odds ratio, *CI* confidence interval, *Hcy* homocysteine

Table 6 ORs (and 95% CIs) of moderate to severe WMH by quintiles of Hcy and folate

Variable	1	2	3	4	*p* trend
Hcy					
Median (μmol/L)	6.94	12.69	16.41	23.04	
Model 1	1.00 (ref)	2.14 (0.87–5.22)	5.22 (1.95–14.00)	5.23 (2.04–13.43)	0.001
Model 2	1.00 (ref)	2.39 (0.91–6.25)	5.83 (2.02–16.83)	8.09 (2.82–23.15)	< 0.001
Model 3	1.00 (ref)	2.69 (0.97–7.46)	6.14 (2.03–18.59)	8.01 (2.70–23.77)	0.001
Folate					
Median (ng/mL)	13.74	9.35	7.07	4.87	
Model 1	1.00 (ref)	4.76 (1.81–12.53)	4.48 (1.73–11.62)	8.14 (2.95–22.41)	< 0.001
Model 2	1.00 (ref)	10.89 (3.29–35.99)	7.90 (2.62–23.79)	18.81 (5.42–65.27)	< 0.001
Model 3	1.00 (ref)	14.34 (4.04–50.92)	10.54 (3.15–35.23)	16.81 (4.74–59.65)	< 0.001

OR odds ratios, *WMHs* white matter hyperintensities, *Hcy* homocysteine, *Ref* reference

ORs and 95% CIs were calculated with the use of the binary logistic regression model. Model 1 was adjusted for age. Model 2 was adjusted for age, vitamin B_{12}, folate, or Hcy. Model 3 was adjusted for age, vitamin B_{12}, cystatin C, hypertension, diabetes, drinking, folate, or Hcy

Test for trend based on variable containing median value for each quintile

to the results of our study, we speculate that DWM aggravates gait disorders in Parkinson's patients by damaging local neuronal networks.

Our present findings reveal an association of Hcy, folate, and WMHs, suggesting that HHcy and low folate levels might contribute to the development of WMHs and perhaps also contribute indirectly to the motor heterogeneity in PD that results from these WMHs.

Limitations

Our research has the following limitations. First, there was no normal control group, which limited our comparison with the general population. Second, the study was a cross-sectional study, and it precluded the investigation of change over time. Finally, this is a single-center study. Our sample size is relatively small, especially the sample of non-PIGD with moderate/severe WMHs, which leads to the imbalance of sample size. This could have affected the meaningfulness of results obtained. All of these limitations will be addressed in future studies by using a larger sample size.

Conclusions

In summary, our data showed a close association between WMHs and Hcy, folate especially in PD-PIGD patients. It can be speculated that higher Hcy and lower folate probably played important roles in the development of WMHs and motor heterogeneity in PD.

Funding This work was financially supported by Jiangsu Provincial Key R&D Program (BE2018658); Jiangsu Provincial Medical Key Discipline Project (ZDXKB2016022); and Suzhou Clinical Research Center of Neurological Disease (Szzx201503).

Compliance with ethical standards

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Conflict of interest The authors declare that they have no conflicts of interests.

References

1. Kotagal V, Albin RL, Muller ML, Koeppe RA, Frey KA, Bohnen NI (2014) Modifiable cardiovascular risk factors and axial motor impairments in Parkinson disease. Neurology 82(17):1514–1520. https://doi.org/10.1212/wnl.0000000000000356
2. Vesely B, Antonini A, Rektor I (2016) The contribution of white matter lesions to Parkinson's disease motor and gait symptoms: a critical review of the literature. J Neural Transm(Vienna, Austria : 1996) 123(3):241–250. https://doi.org/10.1007/s00702-015-1470-9
3. Vesely B, Rektor I (2016) The contribution of white matter lesions (WML) to Parkinson's disease cognitive impairment symptoms: a critical review of the literature. Parkinsonism Relat Disord 22(Suppl 1):S166–S170. https://doi.org/10.1016/j.parkreldis.2015.09.019
4. Grammas P, Martinez J, Miller B (2011) Cerebral microvascular endothelium and the pathogenesis of neurodegenerative diseases. Expert Rev Mol Med 13:e19. https://doi.org/10.1017/s1462399411001918
5. Nelson AR, Sweeney MD, Sagare AP, Zlokovic BV (2016) Neurovascular dysfunction and neurodegeneration in dementia

and Alzheimer's disease. Biochim Biophys Acta 1862(5):887–900. https://doi.org/10.1016/j.bbadis.2015.12.016
6. Sagare AP, Bell RD, Zlokovic BV (2012) Neurovascular dysfunction and faulty amyloid beta-peptide clearance in Alzheimer disease. Cold Spring Harb Perspect Med 2(10). https://doi.org/10.1101/cshperspect.a011452
7. Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV (2015) Establishment and dysfunction of the blood-brain barrier. Cell 163(5):1064–1078. https://doi.org/10.1016/j.cell.2015.10.067
8. Zlokovic BV (2008) The blood-brain barrier in health an Neuron d chronic neurodegenerative disorders. Neuron 57(2):178–201. https://doi.org/10.1016/j.neuron.2008.01.003
9. DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Garner J, Jack L, Carmelli D (1999) Predictors of brain morphology for the men of the NHLBI twin study. Stroke 30(3):529–536
10. Dufouil C, Chalmers J, Coskun O, Besancon V, Bousser MG, Guillon P, MacMahon S, Mazoyer B, Neal B, Woodward M, Tzourio-Mazoyer N, Tzourio C (2005) Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) magnetic resonance imaging substudy. Circulation 112(11):1644–1650. https://doi.org/10.1161/circulationaha.104.501163
11. van Harten B, Oosterman JM, Potter van Loon BJ, Scheltens P, Weinstein HC (2007) Brain lesions on MRI in elderly patients with type 2 diabetes mellitus. Eur Neurol 57(2):70–74. https://doi.org/10.1159/000098054
12. Gustafson DR, Steen B, Skoog I (2004) Body mass index and white matter lesions in elderly women. An 18-year longitudinal study. Int Psychogeriatr 16(3):327–336
13. Jagust W, Harvey D, Mungas D, Haan M (2005) Central obesity and the aging brain. Arch Neurol 62(10):1545–1548. https://doi.org/10.1001/archneur.62.10.1545
14. Knopman DS, Mosley TH, Catellier DJ, Sharrett AR (2005) Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. Neurology 65(6):876–881. https://doi.org/10.1212/01.wnl.0000176074.09733.a8
15. Cervellati C, Romani A, Seripa D, Cremonini E, Bosi C, Magon S, Passaro A, Bergamini CM, Pilotto A, Zuliani G (2014) Oxidative balance, homocysteine, and uric acid levels in older patients with late onset Alzheimer's disease or vascular dementia. J Neurol Sci 337(1–2):156–161. https://doi.org/10.1016/j.jns.2013.11.041
16. Song IU, Kim JS, Park IS, Kim YD, Cho HJ, Chung SW, Lee KS (2013) Clinical significance of homocysteine (Hcy) on dementia in Parkinson's disease (PD). Arch Gerontol Geriatr 57(3):288–291. https://doi.org/10.1016/j.archger.2013.04.015
17. Kirbas S, Kirbas A, Tufekci A, Cumhur Cure M, Cakmak S, Yazici T, Cure E (2016) Serum levels of homocysteine, asymmetric dimethylarginine and nitric oxide in patients with Parkinson's disease. Acta Clin Belg 71(2):71–75. https://doi.org/10.1080/17843286.2016.1138592
18. Rodriguez-Oroz MC, Lage PM, Sanchez-Mut J, Lamet I, Pagonabarraga J, Toledo JB, Garcia-Garcia D, Clavero P, Samaranch L, Irurzun C, Matsubara JM, Irigoien J, Bescos E, Kulisevsky J, Perez-Tur J, Obeso JA (2009) Homocysteine and cognitive impairment in Parkinson's disease: a biochemical, neuroimaging, and genetic study. Mov Disord : Off J Mov Disord Soc 24(10):1437–1444. https://doi.org/10.1002/mds.22522
19. Bhatia P, Singh N (2015) Homocysteine excess: delineating the possible mechanism of neurotoxicity and depression. Fundam Clin Pharmacol 29(6):522–528. https://doi.org/10.1111/fcp.12145
20. Curro M, Gugliandolo A, Gangemi C, Risitano R, Ientile R, Caccamo D (2014) Toxic effects of mildly elevated homocysteine concentrations in neuronal-like cells. Neurochem Res 39(8):1485–1495. https://doi.org/10.1007/s11064-014-1338-7
21. Scott TM, Tucker KL, Bhadelia A, Benjamin B, Patz S, Bhadelia R, Liebson E, Price LL, Griffith J, Rosenberg I, Folstein MF (2004) Homocysteine and B vitamins relate to brain volume and white-matter changes in geriatric patients with psychiatric disorders. Am J Geriatr Psychiatry : Off J Am Assoc Geriatr Psychiatry 12(6):631–638. https://doi.org/10.1176/appi.ajgp.12.6.631
22. Vermeer SE, van Dijk EJ, Koudstaal PJ, Oudkerk M, Hofman A, Clarke R, Breteler MM (2002) Homocysteine, silent brain infarcts, and white matter lesions: the Rotterdam Scan Study. Ann Neurol 51(3):285–289
23. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55(3):181–184
24. Zijlmans JC, Daniel SE, Hughes AJ, Revesz T, Lees AJ (2004) Clinicopathological investigation of vascular parkinsonism, including clinical criteria for diagnosis. Mov Disord : Off J Mov Disord Soc 19(6):630–640. https://doi.org/10.1002/mds.20083
25. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord : Off J Mov Disord Soc 25(15):2649–2653. https://doi.org/10.1002/mds.23429
26. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I, Stern M, Tanner C, Weiner W, Parkinson Study Group (1990) Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 40(10):1529–1534
27. Feng L, Isaac V, Sim S, Ng TP, Krishnan KR, Chee MW (2013) Associations between elevated homocysteine, cognitive impairment, and reduced white matter volume in healthy old adults. Am J Geriatr Psychiatry : Off J Am Assoc Geriatr Psychiatry 21(2):164–172. https://doi.org/10.1016/j.jagp.2012.10.017
28. Kloppenborg RP, Geerlings MI, Visseren FL, Mali WP, Vermeulen M, van der Graaf Y, Nederkoorn PJ (2014) Homocysteine and progression of generalized small-vessel disease: the SMART-MR study. Neurology 82(9):777–783. https://doi.org/10.1212/wnl.0000000000000168
29. Duan W, Ladenheim B, Cutler RG, Kruman II, Cadet JL, Mattson MP (2002) Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic neurons in models of Parkinson's disease. J Neurochem 80(1):101–110
30. Haghdoost-Yazdi H, Fraidouni N, Faraji A, Jahanihashemi H, Sarookhani M (2012) High intake of folic acid or complex of B vitamins provides anti-parkinsonism effect: no role for serum level of homocysteine. Behav Brain Res 233(2):375–381. https://doi.org/10.1016/j.bbr.2012.05.011
31. Zhang CE, Wei W, Liu YH, Peng JH, Tian Q, Liu GP, Zhang Y, Wang JZ (2009) Hyperhomocysteinemia increases beta-amyloid by enhancing expression of gamma-secretase and phosphorylation of amyloid precursor protein in rat brain. Am J Pathol 174(4):1481–1491. https://doi.org/10.2353/ajpath.2009.081036
32. Zhuo JM, Portugal GS, Kruger WD, Wang H, Gould TJ, Pratico D (2010) Diet-induced hyperhomocysteinemia increases amyloid-beta formation and deposition in a mouse model of Alzheimer's disease. Curr Alzheimer Res 7(2):140–149
33. Lee SJ, Kim JS, Lee KS, An JY, Kim W, Kim YI, Kim BS, Jung SL (2009) The severity of leukoaraiosis correlates with the clinical phenotype of Parkinson's disease. Arch Gerontol Geriatr 49(2):255–259. https://doi.org/10.1016/j.archger.2008.09.005
34. Bohnen NI, Muller ML, Zarzhevsky N, Koeppe RA, Bogan CW, Kilbourn MR, Frey KA, Albin RL (2011) Leucoaraiosis, nigrostriatal denervation and motor symptoms in Parkinson's disease. Brain : J Neurol 134(Pt 8):2358–2365. https://doi.org/10.1093/brain/awr139
35. Herman T, Rosenberg-Katz K, Jacob Y, Auriel E, Gurevich T, Giladi N, Hausdorff JM (2013) White matter hyperintensities in

Parkinson's disease: do they explain the disparity between the postural instability gait difficulty and tremor dominant subtypes? PLoS One 8(1):e55193. https://doi.org/10.1371/journal.pone.0055193

36. Song IU, Kim YD, Cho HJ, Chung SW (2013) The effects of silent cerebral ischemic lesions on the prognosis of idiopathic Parkinson's disease. Parkinsonism Relat Disord 19(8):761–763. https://doi.org/10.1016/j.parkreldis.2013.04.006
37. Shine JM, Matar E, Ward PB, Frank MJ, Moustafa AA, Pearson M, Naismith SL, Lewis SJ (2013) Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia. Brain J Neurol 136(Pt 12): 3671–3681. https://doi.org/10.1093/brain/awt272
38. Whitwell JL, Master AV, Avula R, Kantarci K, Eggers SD, Edmonson HA, Jack CR Jr, Josephs KA (2011) Clinical correlates of white matter tract degeneration in progressive supranuclear palsy. Arch Neurol 68(6):753–760. https://doi.org/10.1001/archneurol.2011.107
39. de Laat KF, Tuladhar AM, van Norden AG, Norris DG, Zwiers MP, de Leeuw FE (2011) Loss of white matter integrity is associated with gait disorders in cerebral small vessel disease. Brain : J Neurol 134(Pt 1):73–83. https://doi.org/10.1093/brain/awq343
40. de Groot JC, de Leeuw FE, Oudkerk M, van Gijn J, Hofman A, Jolles J, Breteler MM (2000) Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol 47(2): 145–151