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ORIGINAL RESEARCH

Application of Periventricular White Matter Hyperintensities Combined with Homocysteine into Predicting Mild Cognitive Impairment in Parkinson's Disease

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Purpose: To verify the associations between white matter hyperintensities (WMHs), plasma homocysteine (Hcy) levels, and mild cognitive impairment (MCI) in Parkinson's disease (PD) patients and evaluate the predictive value of combination of WMHs and plasma Hcy levels for MCI.

Patients and methods: In this study, 387 patients with PD were divided into MCI group and non-MCI group. Their cognition was evaluated with a comprehensive neuropsychological evaluation including 10 tests. Five cognitive domains, including the memory, attention/working memory, visuospatial, executive and language domains, were evaluated using two tests for each domain. MCI was determined when at least two tests demonstrated abnormal results, either one impaired test in two different cognitive domains or two impaired tests in a single cognitive domain. Multivariate analysis was performed to determine risk factors for MCI in PD patients. The receiver operating characteristic (ROC) curve was employed to assess the predictive values, and the *Z* test was employed to compare the area under curve (AUC).

Results: MCI was identified in 195 PD patients with an incidence of 50.4%. Multivariate analysis results showed that PWMHs (OR: 5.162, 95% CI: 2.318~9.527), Hcy levels (OR: 1.189, 95% CI: 1.071~1.405) and MDS-UPDRS part III score (OR: 1.173, 95% CI: 1.062~1.394) were independently correlated with MCI in PD patients after adjusting for confounders. ROC curves showed that the AUCs of PWMHs, Hcy levels and their combination were 0.701 (SE: 0.026, 95% CI: 0.647~0.752), 0.688 (SE: 0.027, 95% CI: 0.635~0.742) and 0.879 (SE: 0.018, 95% CI: 0.844~0.915), respectively. *Z* test showed that the AUC of combination prediction was significantly higher than those of individual predictions (0.879 vs 0.701, Z=5.629, P<0.001; 0.879 vs 0.688, Z=5.886, P<0.001).

Conclusion: The combination of WMHs and plasma Hcy levels could be applied in the prediction of MCI in PD patients.

Keywords: Parkinson's disease, mild cognitive impairment, white matter hyperintensities, homocysteine, prediction

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder following Alzheimer disease, affecting 2–3% of adults with an age of greater than 65 years.[1] Cognitive impairment is one of the most common non-motor symptoms of PD, which manifests the deficits occurring in several cognitive domains, including language, executive function/attention, memory and visuospatial ability.[2] A meta-analysis demonstrates that the pooled prevalence of mild cognitive impairment (MCI) was 40% in a total sample size of 7053 patients with PD.[3] MCI in early PD can increase the risk of progressing to early PD dementia, leading to increased mortality.[4,5] Accurate prediction for MCI is helpful for risking stratify patients.

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As a consequence of cerebral small-vessel disease, white matter hyperintensities (WMHs) are described as areas of increased signal demonstrated by fluid-attenuated inversion recovery (FLAIR) or T2-weighted magnetic resonance images. The incidence of WMHs is 30–55% in normal older adults and significantly elevated in PD patients.[6,7] WMHs are divided into deep white matter hyperintensities (DWMHs) and periventricular white matter hyperintensities (PWMHs).[8] According to recent studies, PWMHs are associated with MCI in early PD while total WMHs and DWMHs are not.[9,10] Therefore, PWMHs can be applied in the prediction of MCI in early PD.

Homocysteine (Hcy) is a heterogeneous amino acid cysteine and involved in the methionine metabolism as an important intermediate.[11] Elevated plasma Hcy levels (≥15μmol/L), defined as hyperhomocysteinemia, can have toxic effects on blood vessels and neurons, including oxidative damage and endothelial dysfunction. It is well-established that plasma Hcy levels elevate significantly in PD patients compared with healthy controls,[12–17] which can increase the risk for cognitive impairment and brain atrophy of PD patients.[15–17] However, some reports show that hyperhomocysteinemia is not correlated with cognitive deterioration, neuropsychiatric disorders, depression and dementia among PD patients. In this study, we verified the associations between WMHs, plasma Hcy levels, and MCI in PD patients, and further evaluated the predictive value of combination of WMHs and plasma Hcy levels for MCI, aiming for providing an accurate prediction tool for MCI in PD patients.

Patients and Methods

Participants

Between July 2019 and September 2021, a consecutive cohort of patients with PD visiting Chongqing University Jiangjin Hospital was prospectively recruited. This study was approved by the Ethical Committee of Chongqing University Jiangjin Hospital (JJ2020017029) and performed conforming to the guidelines of the *Declaration of Helsinki*, and all participants provided written informed consents.

The inclusion criteria were ① newly diagnosed patients with PD according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria;[18] ② meeting de novo criteria, ie, L-dopa exposure no longer than 2 weeks and not within 4 weeks prior to study recruitment; ③ ranging from 40 to 85 years old. The exclusion criteria included ① medication-induced PD; ② signs or symptoms of progressive supranuclear palsy or multiple system atrophy according to consensus criteria;[19,20] ③ known severe normal-pressure hydrocephalus (NPH) or vascular encephalopathy as demonstrated by MRI alone; ④ receiving drugs within the past 3 months that could influence serum Hcy, blood lipid and Cys C levels; ⑤ kidney and liver dysfunction; severe cardiovascular, respiratory, haematologic system, wasting or nutritional metabolism diseases. MRI and baseline cognitive evaluation were performed in all participants. Patients with PD dementia were excluded by clinical dementia rating (CDR) ≥ 0.5 points.

Data Collection and Clinical Evaluations

Clinical, demographic and laboratory data of participants were collected, including age, gender, body mass index (BMI), hypertension, diabetes, hyperlipidemia, smoking, disease duration, duration of education, current non-PD and PD medications, homocysteine (Hcy), total cholesterol (TC), triglyceride (TG), cystatin C (Cys C), apolipoprotein B (Apo B), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). Clinical evaluations, including Hoehn and Yahr staging and Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), were carried out by trained researchers.

Neuropsychological Evaluation and Definition of MCI in PD

The cognition of participants was evaluated with a comprehensive neuropsychological evaluation including 10 tests. Five cognitive domains, including the memory, attention/working memory, visuospatial, executive and language domains, were evaluated using two tests for each domain. Rey-Osterrieth complex figure delayed recall and Alzheimer's Disease Assessment Scale-cognitive subscale word list learning with delayed recall were used to

measure the memory domain, Wechsler Memory Scale-Fourth Edition (WMSIV) symbol span and Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) digit span backward were used to measure the attention/working memory domain, Benton Judgement of Line Orientation and Rey-Osterrieth complex figure copying test were used to measure the visuospatial domain, Frontal Assessment Battery and Fruit Fluency were used to measure the executive domain, and WAIS-IV similarities and Boston Naming Test were used to measure the language domain. MCI was identified in PD patients when at least two tests demonstrated abnormal results, either one impaired test in two different cognitive domains or two impaired tests in a single cognitive domain.

Acquisition of MRI and Quantification of WMHs

The 3T Skyra system (Siemens Healthineers-Erlangen, Germany) was employed to conduct the MRI. The following parameters were used to obtain T1-weighted Magnetization Prepared-RApid Gradient Echo (MP RAGE) images, including 1900/2.44 ms of repetition time (TR)/echo time (TE), 256×253 of matrix, 900 ms of inversion time (TI), 250×250 of field of view and 1 mm of slice thickness. The following parameters were used to obtain fluid-attenuated inversion-recovery (FLAIR) images, including 7000/132 ms of TR/TE, 256×256 of matrix, 2.2102e + 03 ms of TI, 220×220 of field of view, 150° of flip angle and 4 mm of slice thickness.

Custom scripts in Matlab R2017b (The MathWorks, Natick, MA, USA) and SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) were used to conduct pre-processing of imaging. Firstly, a-priori SPM8 tissue probability map template was used to segment T1-weighted images into tissue classes that were then coregistered to FLAIR images. Secondly, the non-uniformity intensity correction and region-wise segmentation of white matter tissue for the FLAIR images were performed through "New Segment" function in the SPM8.[21] Finally, WMH values of the total brain and periventricular region were calculated according to the segmented FLAIR images.

Measurement of Laboratory Indices

Peripheral vein blood of 4 mL was collected in all participants after fasting for at least 12 h. The blood was then centrifuged at 4000 rpm for 20 min to obtain the serum, and the serum was measured for Hcy, TC, TG, Cys C, Apo B, HDL-C and LDL-C levels with a Cobas® 8000 automatic biochemical analyzer (Roche, Mannheim, Germany). The necessary controls and reagents for measurement were provided by Roche.

Statistical Analysis

Statistical analysis was conducted with the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., USA), and a two-sided $P<0.05$ was considered statistically significant. Continuous data were assessed for normality through Kolmogorov–Smirnov test. Among them, the normally distributed ones were expressed as mean±standard deviation (SD) and compared for intergroup differences through Independent-Samples *t*-test, and the non-normally distributed ones were expressed as median and interquartile range and compared for intergroup differences through Mann–Whitney *U*-test. Categorical data were expressed as percentages/ratios (%) and compared for intergroup differences through chi-square test. The variables with two-sided $P<0.10$ in univariate analysis were included in binary logistic regression model to determine risk factors for MCI in PD patients. The receiver operating characteristic (ROC) curve was employed to assess the predictive values, and the *Z* test was employed to compare the area under curve (AUC).

Results

General Data

During the study period, 429 PD patients were recruited. Among them, 21 patients were excluded due to refusal of study participation, 12 patients due to presence of signs or symptoms for other (atypical) disease, 4 patients due to prior medications for PD, 3 patients due to occurrence of NPH, and 2 patients were excluded occurrence of predominant postural tremor and polyneuropathy. Finally, a total of 387 patients were included in this study.

These 387 patients contained 221 males (57.1%) and 166 females (42.9%) with an average age of (63.68±8.12) years old. The average disease duration was (13.06±7.75) months, and average total brain and periventricular WMH volumes were 1.16±0.65 and 1.03±0.52 cm^3, respectively. MCI was determined in 195 PD patients with an incidence of 50.4%.

Univariate Analysis

Univariate analysis was performed between PD patients with MCI and without MCI. The results (Table 1) demonstrated that age, duration of education, disease duration, MDS-UPDRS part III score, hypertension, total brain WMHs, PWMHs, Hcy and Cys C levels were statistically different (P <0.05), while the rest variables were not (P >0.05). But the P value of hyperlipidemia was <0.10.

Multivariate Analysis

In order to determine risk factors for MCI in PD patients, age, duration of education, disease duration, MDS-UPDRS part III score, hypertension, total brain WMHs, PWMHs, hyperlipidemia, Hcy and Cys C levels were included in binary logistic regression model for multivariate analysis. Multivariate analysis results showed that PWMHs [odds ratio (OR): 5.162, 95% confidence interval (CI): 2.318~9.527, P<0.001], Hcy levels (OR: 1.189, 95% CI: 1.071~1.405, P=0.008) and MDS-UPDRS part III score (OR:1.173, 95% CI: 1.062~1.394, P=0.019) were independently correlated with MCI in PD patients after adjusting for confounders, including age, duration of education, disease duration, hypertension, total brain WMHs, hyperlipidemia and Cys C levels (all P>0.05).

Predictive Values

The ROC curve was used to assess the predictive values of PWMHs, Hcy levels and their combination for MCI in PD patients, and the results (Figure 1) showed that the AUCs of PWMHs, Hcy levels and their combination were 0.701

Table 1 Univariate Analysis Results Between PD Patients with MCI and Without MCI

	PD Patients (387)	MCI Group (195)	Non-MCI Group (192)	χ^2/t	P
Age(years, mean±SD)	63.68±8.12	65.74±8.32	61.59±7.91	5.029	<0.001
Male(n, %)	221(57.1%)	109(55.9%)	112(58.3%)	0.234	0.628
BMI(Kg/m^2, mean±SD)	23.86±3.42	23.95±3.39	23.77±3.46	0.517	0.618
Hypertension	173(44.7%)	99(50.8%)	74(38.5%)	5.851	0.016
Diabetes	67(17.3%)	39(20.9%)	28(14.7%)	1.983	0.159
Hyperlipidemia	190(49.1%)	105(53.8%)	85(44.3%)	3.549	0.060
Smoking	75(19.4%)	41(21.0%)	34(17.7%)	0.681	0.409
Disease duration(months, mean±SD)	13.06±7.75	12.18±7.33	13.96±8.17	−2.255	0.027
Duration of education(years, mean±SD)	10.74±4.06	10.17±3.98	11.32±4.15	−2.782	0.006
MDS-UPDRS part III score(mean±SD)	20.96±9.86	22.57±10.29	19.32±9.43	3.240	0.001
Hoehn and Yahr stage(mean±SD)	1.77±0.47	1.80±0.48	1.74±0.46	1.256	0.214
Levodopa equivalent daily dose(mg/d, mean±SD)	159.32±60.26	158.39±61.54	160.26±58.97	−0.305	0.774
Total brain WMHs(cm^3, mean±SD)	1.16±0.65	1.25±0.75	1.07±0.54	2.713	0.008
PWMHs(cm^3, mean±SD)	1.03±0.52	1.22±0.59	0.84±0.45	7.131	<0.001
Hcy(μmol/L, mean±SD)	14.94±4.95	16.18±4.76	13.69±5.15	4.937	<0.001
TC(mmol/L, mean±SD)	4.22±1.03	4.29±1.08	4.15±0.97	1.342	0.185
TG(mmol/L, mean±SD)	1.30±0.57	1.26±0.53	1.32±0.61	−1.032	0.315
Cys C(mg/L, mean±SD)	0.91±0.36	0.95±0.33	0.86±0.40	2.412	0.017
Apo B(g/L, mean±SD)	0.85±0.30	0.86±0.31	0.83±0.29	0.983	0.337
HDL-C(mmol/L, mean±SD)	1.27±0.57	1.24±0.53	1.31±0.62	−1.193	0.242
LDL-C(mmol/L, mean±SD)	2.66±1.10	2.70±1.15	2.62±1.04	0.718	0.475

Abbreviations: PD, Parkinson's disease; MCI, mild cognitive impairment; BMI, body mass index; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; WMHs, white matter hyperintensities; PWMHs, periventricular white matter hyperintensities; Hcy, homocysteine; TC, total cholesterol; TG, triglyceride; Cys C, cystatin C; Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

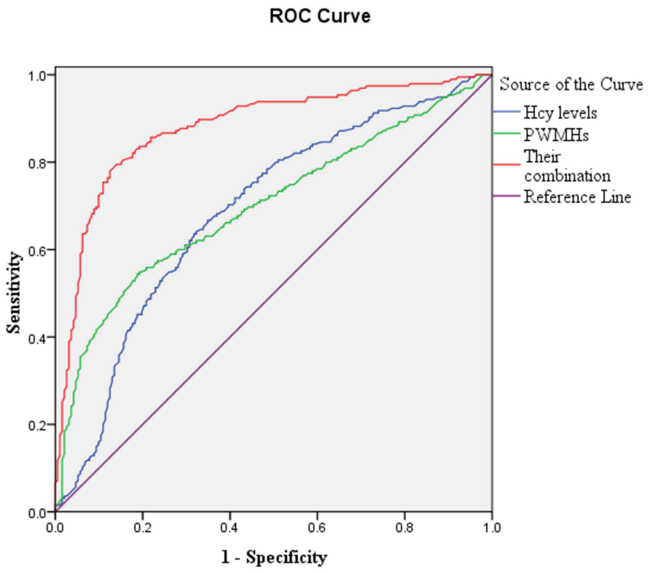

Figure 1 ROC curves of PWMHs, Hcy levels and their combination in predicting MCI in PD patients.

[standard error (SE): 0.026, 95% confidence interval (CI): 0.647~0.752, P<0.001], 0.688 (SE: 0.027, 95% CI: 0.635~0.742, P<0.001) and 0.879 (SE: 0.018, 95% CI: 0.844~0.915, P<0.001), respectively. Z test showed that the AUC of combination prediction was significantly higher than those of individual predictions (0.879 vs 0.701, Z=5.629, P<0.001; 0.879 vs 0.688, Z=5.886, P<0.001). The ROC curve of combination prediction was drawn with the probability derived from logistic regression model. Their clinical utility indexes were demonstrated in Table 2. According to Table 2, the clinical utility indexes of combination prediction were relatively high, and therefore it could be applied in the prediction of MCI in PD patients.

Discussion

WMHs are mainly induced by chronic diffuse subclinical ischemia which can influence all regions of the brain but primarily affects periventricular regions.[22,23] The restriction of blood supply for the brain tissue can cause glucose and oxygen shortage, consequently leading to disturbance of cellular metabolism. WMHs, reflecting axonal loss and demyelination, are frequently observed in the elderly people and patients with Alzheimer's disease.[23] Studies have shown that WMHs in PD patients are correlated with orthostatic hypotension (ie, a drop of blood pressure when going from the supine to upright position),[24,25] the most common cardiovascular autonomic dysfunction of PD patients.[25,26] This correlation is in favor of the vascular hypothesis that recurrent hypotension can result in cerebral hypoperfusion, which can in turn induce anoxic damage to the vulnerable brain areas and finally result in cognitive disorders.[27] Additionally, PD itself and degenerative processes correlated with aging may also play a role in white matter changes.[25] The incidence of WMHs is 30%~55% in normal older adults and significantly elevated in PD patients.[6,7] Early WMHs have been demonstrated to be associated with cognitive disorders in PD patients.[28–30]

Table 2 Clinical Utility Indexes of PWMHs, Hcy Levels and Their Combination for the Prediction of MCI in PD Patients

	Best Cut-Off	Sensitivity	Specificity	Accuracy	FPR	FNR	PPV	NPV
Combination prediction		85.1%	88.5%	86.8%	11.7%	14.6%	88.3%	85.4%
Periventricular WMHs	1.10 cm^3	67.2%	61.5%	64.3%	36.1%	35.2%	63.9%	64.8%
Hcy levels	15.23 μmol/L	57.4%	70.3%	63.8%	33.7%	38.1%	66.3%	61.9%

Abbreviations: WMHs, white matter hyperintensities; Hcy, homocysteine; FNR, false negative rate; FPR, false positive rate; NPV, negative predictive value; PPV, positive predictive value.

However, this conclusion remains controversial. According to recent studies, PWMHs are associated with MCI in early PD while total WMHs and DWMHs are not.[9,10] In addition, Sunwoo et al and Liu et al showed that the burden of WMHs could be applied in the prediction from MCI to dementia in PD patients.[31,32] In this study, PWMHs were independently associated with MCI in PD patients while total WMHs were not, which was consistent with the results of Huang et al.

The metabolism of Hcy included multiple metabolic pathways, and the most important pathway is methylation facilitated by vitamin B_{12} and folate.[33] The dysregulation of this metabolic pathway can lead to accumulation of Hcy.[34] Studies demonstrate that Hcy levels can be influenced by many factors, including age, diet, gene, sex, medication and diet.[34,35] As a glutamate receptor agonist, Hcy can experience auto-oxidation, leading to the disruption of redox homeostasis.[36] In neuronal cells, increasing oxidative stress induced by the disruption of the redox signal pathway can potentially cause their apoptosis, which is correlated with brain atrophy. Elevation of plasma Hcy levels has been shown to be a risk factor of cognitive decline and dementia in the normal adults and correlated with MCI, depression, vascular dementia and Alzheimer's disease.[37–41]

In PD patients, plasma Hcy levels are significantly elevated compared with healthy controls, which is associated with the increased risk of cognitive impairment and brain atrophy. Song et al showed that plasma Hcy levels were higher in PD patients with dementia than in healthy controls and PD patients without dementia, and concluded that plasma Hcy levels were associated with the cognitive decline of PD patients.[15] Zou et al showed that serum Hcy levels were higher in PD and vascular parkinsonism patients with dementia than in healthy controls, and indicated that serum Hcy levels were correlated with the severity of PD and vascular parkinsonism patients with dementia, including gastrointestinal/mood symptoms, declined cognition and motor dysfunction.[14] Fu et al showed that PD patients with cognitive impairment exhibited the highest Hcy levels compared with sex- and age-matched controls and PD patients with normal cognition, suggesting that Hcy played a role in the pathophysiological of cognitive impairment among PD patients.[17] Dong et al also showed that plasma Hcy levels of PD patients were significantly increased compared with healthy controls in China, and moreover the cognitive status of PD patients could influence plasma Hcy levels.[42] However, some reports have demonstrated the opposite results. Maria et al found that plasma Hcy levels were significantly elevated in PD patients compared with controls, but there were no significant differences between PD patients with normal cognition, MCI and dementia.[43] Kocer et al demonstrated that there was no association between serum Hcy levels and the cognitive status, severity of motor symptoms and stage of the disease, etc.[44]

In this study, plasma Hcy levels were higher in PD patients with MCI than in PD patients without MCI, and moreover multivariate analysis confirmed an independent association between Hcy levels and MCI in PD patients. We further evaluated the predictive values of PWMHs, Hcy levels and their combination to provide an accurate prediction tool for MCI in PD patients. The ROC curves showed that the AUC of combination prediction was significantly higher than those of individual predictions. Moreover, the clinical utility indexes of combination prediction were relatively high (85.1% of sensitivity, 88.5% of specificity and 86.8% of accuracy), and therefore it could be applied in the prediction of MCI in PD patients.

There were two main limitations in this study. First, the prevalence of MCI in this study was higher than that has been reported elsewhere, which was associated with selection bias. Second, this study was a cross-sectional analysis rather than a longitudinal analysis.

Conclusion

PWMHs and Hcy levels were independently correlated with MCI in PD patients, and their combination could be applied in the prediction of MCI in PD patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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