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Original Article

Vascular risk factors aggravate the progression of Parkinson's disease: a five-year follow-up study in Chinese patients

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Abstract: Objective: Some studies have found that vascular risk factors were related to an increased risk of Parkinson's disease. In order to investigate the comorbidities of the vascular risk factors with PD and their impact on PD progression, we launched a five-year follow-up study in 247 outpatients with probable PD. Methods: The incidence of vascular risk factors including hypertension, diabetes, hypercholesterolemia, hyperhomocysteinemia and carotid atherosclerotic plaque analyzed. The Hoen and Yahr score with and without vascular risk factors were compared at initial and at final evaluation. Results: Multiple regression analysis showed that age, hypertension and hyperhomocysteinemia were significant variables that are associated with the Hoen and Yahr scales. Younger patients with hypertension or hyperhomocysteinemia showed a greater increasing in the Hoen and Yahr score. There were no significant correlations among the Hoen and Yahr score with sex, initial of the Hoen and Yahr score, diabetes, hypercholesterolemia or carotid atherosclerotic plaque. Conclusion: The vascular risk factors are common comorbidities of PD. Younger, more educated patients are more likely to have quicker dyskinesia decline. In addition, hypertension and hyperhomocysteinemia may aggravate the progression of PD. The prevention and treatment of hypertension and hyperhomocysteinemia are important for PD patients.

Keywords: Parkinson's disease, cognition, progression, vascular risk factors

Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder. Clinically, PD is defined by abnormal cardinal motor features, such as tremor, rigidity, bradykinesia and postural instability [1, 2]. The symptoms are characterized by the loss of approximately 50% of dopaminergic (DA) neurons in substantia nigra (SN), and further resulting in depletion of striatal dopamine about 70-80%, but the symptoms indicative of the compensatory mechanisms enabling "normal" functioning despite the ongoing deterioration [3, 4]. Other neuronal populations in the brain stem, subcortical and cortical regions are also affected by PD [5, 6]. Additionally, PD is associated with non-motor symptoms that can co-occur or precede the motor manifestations by many years [7]. They comprise cognitive and psychiatric problems, which result in impaired olfaction, sleep disturbances, and autonomic insufficiency [8, 9].

Compelling evidences have suggest that vascular risk factors such as hypertension, diabetes, hypercholesterolemia, atrial fibrillation are related with increased risk of Alzheimer's disease [10-12], they also play an important role in the progression of Alzheimer's disease and development of dementia, however, it remains unclear whether such vascular factors play a role in the attack and progression of the Parkinson's disease. Wolozin *et al* suggested that medications used to treat these risk factors are also associated with a reduced incidence of dementia and Parkinson's disease [12]. The vascular hypothesis of PD, which proposes that dysfunction of the neurovascular unit contributes to the pathogenesis of PD have be mentioned, but it is difficult to draw a definitive conclusion. With the aging of the population, China has a huge prevalence of PD [13]. Because of the differences in race, economic level, lifestyles, vascular risk factors and their effects on the progression of PD may differ from those in western countries, further pro-

Table 1. Clinical and demographic characteristics of PD patients at initial evaluation

No. of patients	247
Mean age ± SD, y	71.5±7.7
Sex (male), n (%)	111 (44.9%)
Mean course ± SD, y	4.1±2.5
Education	
Illiteracy, n (%)	24 (9.7%)
Primary school, n (%)	51 (20.69%)
Middle school and above, n (%)	82 (33.2%)
College and above, n (%)	90 (36.4%)
MMSE score at initial evaluation	20.1±2.9
HY scale at initial evaluation	2.1±1.3

MMSE: Mini-Mental State Examination; HY scale: Hoehn and Yahr scale.

Table 2. Vascular risk factors of PD patients at initial evaluation

VRF	N (%)
Hypertension	92 (37.2%)
Diabetes	78 (31.6%)
Hypercholesterolemia	50 (20.2%)
Hyperhomocysteinemia	93 (37.7%)
Carotid atherosclerostic plaque	96 (38.9%)

spective studies on PD patients with a longer follow-up period in different regions and ethnic backgrounds are needed. The purpose of this study was to determine whether socio-demographic factors as well as common vascular risk factors, could contribute to the onset and progression of PD in Chinese patients.

Subjects and methods

In this study, we recruited consecutive PD patients (age of 70 years) followed up in the Department of Neurology of Municipal Hospital of Taizhou, China. This study was approved by Hospital Review Board and was conducted in accordance with good clinical practice and the guiding principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to admission to the study.

Diagnosis and data collection

A clinical diagnosis of probable or definite PD was performed according to the UK brain bank criteria [14]. Only patients who had bradykinesia and at least two of rigidity, rest tremor and postural instability were included. All patients were investigated with either brain CT or MRI. Diagnosis of psychiatric disorders was established by the patient's treating psychiatrists using the Diagnostic and Statistical Manual of the Mental Disorders, 4th edition (American Psychiatric Association, 1994). Dementia was evaluated using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) (scores < 24 were considered indicative of dementia). Dementia and depression were used for adjustments in the multiple logistic analyses together with age, sex, and duration of the disease.

In order to only include patients suffering from PD and to exclude all other patients being misdiagnosed or suffering from vascular parkinsonism (VP), patients who developed parkinsonism after a cerebrovascular accident or suffered from neoplastic or other disabling diseases (with movement impairment) were excluded, and only patients with silent infarcts or minor stroke and no residual disability were included in the study. We also excluded patients with prominent clinical features of VP such as acute onset, stepwise progression, early lower body involvement and failure to respond to levodopa therapy.

The presence of hypertension and diabetes was defined according to diagnosis and subsequent treatment by an experienced physician at hospital, or according to a relative's report of previous and ongoing treatment for the respective conditions. Each diagnosis was based on the clinical guidelines published by the Chinese Medical Association. The hypercholesterolemia was defined as plasma cholesterol level > 5.2 mmol/L. Hyperhomocysteinemia was defined as plasma homocysteine > 15 μmol/L. Carotid atherosclerostic plaques was defined as Intima-media thickness (IMT) > 1.3 mm.

Severity of motor symptoms was measured by means of the activities-of-daily living and motor subscales of the Unified Parkinson's Disease Rating Scale (UPDRS part II and III, respectively) [15, 16], and related staging was assessed by the Hoehn and Yahr (HY) scale [17, 18]. In addition, we calculated disease progression index defined by ratio between HY stage and disease duration. We also recorded the presence of dyskinesia. All patients enrolled were continuously or intermittently treated with cholinesterase inhibitors and/or NMDA receptor antagonist (memantine hydrochloride).

Statistical analysis

Values are expressed as means ± standard deviation or constituent ratio. The relationship between PD with or without vascular risk factors was analyzed by univariate analysis, including t test for association in independent normally distributed continuous data, Chi square test for categorical data. In addition, multiple logistic regression analysis was performed to determine the influence of socio-demographic factors on the PD progression. Independent variables included age, sex, education, HY scales at initial evaluation, and vascular risk factors including hypertension, diabetes, hypercholesterolemia, hyperhomocysteinemia, and carotid atherosclerostic plaque. The dependent variable was HY stage (continuous). A *P*-value of less than 0.05 was considered to indicate a statistically significant difference. The statistical analyses were performed by SPSS 13.0 for Windows.

Results

Enrolled 247 PD patients had a mean age of 71.5±7.7 years. 111 (44.9%) were men and 136 (55.1%) were women. Their education levels were as follows: Illiteracy, 9.7% (24 patients); Primary school, 20.69% (51 patients); Middle school, 33.2%, 82 patients, college and above, 36.4% (90 patients). The courses of disease were 3.6±3.1 years. The mean MMSE and HY scores at initial were 20.1±2.9 and 2.1±1.3, respectively (**Table 1**). All the patients finished the follow-up for 60 months and these patients has no difference in age, gender, education levels, courses and MMSE and HY score at baseline.

As shown in **Table 2**, the incidences of vascular risk factors in these PD patients were: hypertension, 37.2% (92 patients); diabetes, 31.6% (78 patients); and hypercholesterolemia, 20.2% (50 patients); hyperhomocysteinemia, 37.3% (93 patients); carotid atherosclerostic plaque, 38.9% (96 patients). Only 33.6% (83 patients) were free from vascular risk factors. All the patients with vascular factors were subjected to medical follow-up. Calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were used for hypertension; oral hypoglycemic drugs were used for diabetes; statins were used for hypercholesterolemia; folvite and vitamin B12 were used for hyperhomocysteinemia.

No significant difference in age, sex, education levels, and course at initial evaluation was found between PD patients with and without vascular risk factors. But significant difference in the scores of MMSE and HY scales between at initial and at final evaluation have been found ($P < 0.05$).

We found that the MMSE scores of patients with vascular risk factors were lower than those of patients without vascular risk factors either at initial evaluation or at final evaluation. By contrast, HY scales of patients with vascular risk factors were higher than those of patients without vascular risk factors either at initial evaluation or at final evaluation (**Table 3**). Multiple regression analysis showed that age, education and hypertension and hyperhomocysteinemia, but not diabetes, hypercholesterolemia, carotid atherosclerostic plaque were significant variables associated with PD progression. Younger, more educated patients with hypertension or hyperhomocysteinemia showed a greater increase in annual HY scores (**Table 4**).

Discussion

Parkinson's disease (PD) is a degenerative disorder of the central nervous system. The motor symptoms of PD begin with the death of dopamine-generating cells in the substantia nigra, a region of the midbrain; the cause of this cell death is unknown [19]. Age of onset and education levels could affect the deterioration of Hoehn and Yarh scores. Evidences have showed that vascular risk factors and disorders may be involved in PD [20, 21]. The issue that whether Parkinson's disease is a neurodegenerative or vascular disorder was still in dispute [22-24]. In accordance with those studies, we confirmed that vascular risk factors, including hypertension, diabetes, hypercholesterolemia, hyperhomocysteinemia and carotid atherosclerotic plaques, are common comorbidities with PD patient. Our study demonstrates that 66.4% PD patients have co-existed with vascular risk factors. Moreover, we further confirmed that younger and more educated patients with PD have faster Hoehn and Yarh scale deterioration; we also found that hypertension or hyperhomocysteinemia rather than diabetes, hypercholesterolemia, or carotid atherosclerostic plaque was associated with faster Hoehn and Yarh scale deterioration.

Table 3. Characteristics of PD patients with and without VRF at initial and final evaluation

Variables	With VRF	Without VRF	*P*
Mean age ± SD, y	71.3±5.8	71.8±6.2	>0.05
Sex (male), n (%)	76 (46.3%)	35 (42.2%)	>0.05
Education			>0.05
Illiteracy, n (%)	17 (70.8%)	7 (29.2 %)	
Primary school, n (%)	30 (58.8%)	21 (41.2%)	
Middle school and above, n (%)	51 (62.2%)	31 (37.8%)	
College and above, n (%)	55 (61.1)	35 (38.9%)	
Mean course ± SD, y	3.7±3.5	3.6±4.1	
MMSE score			
At initial evaluation (n=247)	20.5±4.1	21.1±4.2	>0.05
At final evaluation (n=247)	14.6±4.8	17.2±3.4	<0.05
HY scales			
At initial evaluation (n=247)	2.2±0.7	2.1±0.6	>0.05
At final evaluation (n=247)	3.6±1.1	2.8±0.9	<0.01

Table 4. Effects of variables on annual HY scales change (n=247)

Variables	β	t-value	*P*-value
Age (years)	0.357	4.229	0.007**
Male	-0.025	-0.324	0.74
Education	-0.211	-3.138	0.031*
Initial MMSE score	-0.023	-0.178	0.772
Hypertension	-0.172	-2.116	0.045*
Diabetes	- 0.154	-1.235	0.105
Hypercholesterolemia	-0.112	-1.447	0.315
Hyperhomocysteinemia	-0.155	-2.114	0.033*
Carotid atherosclerostic plaque	0.058	-0.199	0.736

*$P < 0.05$; **$P < 0.01$, β: standardized regression coefficient.

A large number of epidemiological investigations found that blood pressure is one of the important factors influences cognitive function in the elderly. The elevation of blood pressure at middle-aged is an important risk factor for cognitive function impairment and the occurrence of PD at old age [25]. Drug clinical trials also found that controlling blood pressure with antihypertensive medications, on the other hand, can reduce the occurrence of cognitive impairment and slow the progression of PD [26]. The evidences seem to support that high blood pressure promotes the occurrence of PD. Vascular changes linked to hypertension may induce chronic and episodic cerebral hypoperfusion, ischemia and hypoxia, which are possible mechanisms that link cerebrovascular disorders to dementia [27].

Pathologically, PD is characterized by a severe loss of dopaminergic neurons that is visible as depigmentation of the substantia nigra pars compacta in the basal ganglia. Given that the pathogenesis that leads to the selective death of dopaminergic neurons is poorly understood [28, 29], the biological mechanisms linking hypertensive status to PD can only be speculated. First, long-standing elevated BP can cause ischemic cerebrovascular lesions. Clinicopathological studies suggested that cerebral microvascular diseases (eg, white-matter lesions and cerebral amyloid angiopathy) are likely to contribute to the clinical expression and deterioration of idiopathic PD symptomatology [30]. Therefore, hypertension and elevated BP could be linked to PD by affecting the non-dopaminergic subcortical structures. Second, chronic high BP causes hypertensive vasculopathy in the basal ganglia, thalamus, and brain stem [31], which may affect dopaminergic cells in the pars compacta and break the connections between neurons in the substantia nigra and the putamen portion of the striatum. Third, oxidative stress and renin-angiotensin system are common mechanisms leading to both hypertension and PD. Finally, experimental research suggests that cerebral ischemia caused by long-standing hypertension may decrease the expression of β-2 and α-4 subunits of nicotinic acetylcholine receptors, which could activate the dopaminergic pathway [32].

Diabetes is associated with an increased risk of PD [33, 34]. Many clinical epidemiological studies have found that either type 1 or type 2 diabetes is closely related to the occurrence of dementia, including vascular dementia and PD. Our study showed faster progression in PD patients with diabetes, but it did not reach a

statistically significant difference. It may cause by the severity of the disease and the treatment for diabetes. Some studies found that the occurrences of cognitive decline and delay dementia can be slowed as long as the blood sugar levels were controlled, either by oral hypoglycemic drugs or by insulin treatment. The association between diabetes and postural instability as well as gait difficulty persisted after controlling for comorbid hypertension and body mass index. Diabetes may contribute to postural instability and gait difficulty in Parkinson disease through mechanisms other than nigrostriatal dopaminergic denervation [34].

Homocysteine is a newly found risk factor for atherosclerosis and cardio-cerebrovascular disease, its level is associated with the serum concentration of folate and vitamin B12. Some studies have found that high blood level of homocysteine was related to PD [35]. Homocysteine may cause cerebral ischemic lesion through direct or indirect damage to vascular endothelial and blood coagulation system. It has been suggested that breakdown of L-dopa by catechol-O-methyltransferase results in increased homocysteine formation. Therefore, it is reasonable to suggest that management of PD may render increased risk of stroke, heart disease, dementia, and even accelerated nigral degeneration in patients [36].

It is now widely recognized that substantial overlap exists among vascular risk factors and PD. Vascular hypothesis of PD have been further improved. Vascular risk factors lead to blood-brain barrier dysfunction and reduction of cerebral blood flow, initiating a cascade of events that precede dementia.

It should be noted that our study has some limitations. First, we did not assess the duration of vascular risk factors and medications for vascular risk factors which may be associated with progression of disease. Second, the number of cases and the time for follow-up were limited. In spite of these limitations, we conclude that hypertension and hyperhomocysteinemia, in addition to age and education levels, may speed up cognitive disorder. Our findings imply that new strategies that control vascular risk factors may conduce to the prevention of PD. At least till now, it remains controversial whether vascular risk factors are the predictors of PD. Moreover, there is limited direct evidence to support the complex associations between vascular risk factors and PD pathogenesis. As the matter is far from being resolved, further prospective studies will be needed to determine whether control of hypertension or hyperhomocysteinemia may slow down the progression of PD.

Conclusions

To our knowledge, we show vascular risk factors such as hypertension, diabetes, hypercholesterolemia, hyperhomocysteinemia and carotid atherosclerotic plaques are common comorbidities in PD patients. Younger, more educated patients are more likely to have faster dyskinesia decline. In addition, hypertension and hyperhomocysteinemia may also aggravate the progression of PD. Our results suggest that prevention and treatment for hypertension and hyperhomocysteinemia are of vital importance for PD patients.

Disclosure of conflict of interest

None.

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