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Original Article

Correlation between the presenilin1 gene polymorphism and the onset of vascular dementia

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Abstract: Objective: This study aimed to investigate the relationship of the polymorphism rs200165137 in the presenilin1 (PS1) gene with vascular dementia (VD). Methods: A total of 106 patients with VD and 102 healthy elderly patients without dementia were enrolled. The general data and disease histories (hypertension, diabetes and hyperlipidemia) were collected. The levels of serum homocysteine (Hcy), folic acid and vitamin B_{12} were measured, and TaqMan®-miner groove binder (MGB) probes were applied to identify PS1 polymorphism rs200165137. Results: Patients in the VD group were found with a significant increase of Hcy and reduced levels of folic acid and vitamin B_{12} compared to those in the control group ($P<0.05$). The frequency of 1/1 genotype in the VD group was significantly higher than that in the control group ($P<0.01$), whereas the frequency of 2/2 genotype in the former was significantly lower than that in the latter ($P<0.01$). The frequency of 1 allele in the VD group was significantly higher than the control group ($P<0.01$). Significant differences of Hcy, folic acid and vitamin B_{12} levels were found among three PS1 genotypes in the VD group ($P<0.05$). Conclusion: The onset of VD has a correlation with the 1/1 genotype of rs200165137 in the PS1 gene and the gene carrying 1 allele serves as a critical factor for the increased risk of VD.

Keywords: Presenilin1, single nucleotide polymorphism, vascular dementia

Introduction

Vascular dementia (VD), second only to Alzheimer's disease, is a common type of dementia and a type of syndrome primarily characterized by cognitive dysfunction triggered by brain tissue impairment due to a series of cerebrovascular factors such as brain tissue infarction, ischemic encephalopathy and hemorrhagic encephalopathy [1]. According to epidemiological surveys, the prevalence rate of VD is 1-4% in people aged over 65 years old, which is doubles as age increases [2, 3]. With the aging of the population, the incidence rate of VD exhibits an increasing trend annually. Although the disease has been actively treated in clinical practice, the disability rate of VD remains high and the disease not only seriously influences the quality of life of elderly patients, but also brings an extremely heavy burden to families and society. Therefore, the knowledge of the pathogenesis and prevention approaches for VD treatment requires further development. Current studies have indicated that presenilin1 (PS1) activates neural precursor cells and affects their regeneration through the Notch signaling pathway, and thus are essential for the development of nerves and their functional maintenance, all of which are closely associated with cognitive function [4, 5]. In this study, PS1 gene polymorphisms in patients with VD were examined so as to investigate the correlation between the PS1 gene and VD.

Patients and methods

Subjects

VD patients admitted to the Psychiatry Department in the Tongde Hospital of Zhejiang Province from June 2016 to June 2018 were selected. The National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherché et l'Ensei-

Table 1. Information of TaqMan®-miner groove binder (MGB) probes for rs200165137 in the PS1 gene

SNP Reference	rs200531676
Assay Identity Card (ID)	C_190085474_10
Protein ID	NP_000012.1
SNP type	Intron
Context sequence	TTGTTTTCTCCTTTGCATATCTCT[TCT/-]ACTCAGATACCTGGTAGCATATAA

Table 2. Comparison of basic data

Group	n	Age (years old)	Male/female	BMI (kg/m^2)	Hypertension (n)	Diabetes (n)	Hyperlipidemia (n)
Control group	102	60.82±9.78	52/50	23.82±2.78	77	39	40
VD group	106	61.03±9.12	57/49	24.12±3.23	81	40	44
t/x^2		1.456	0.163	0.032	0.024	0.130	0.630
P		0.112	0.687	0.798	0.876	0.719	0.427

gnement en Neurosciences (NINDS-AIREN) criteria were adopted as the diagnostic criteria. Inclusion criteria: (1) cognitive impairment of a vascular nature with brain MRI showing the presence of lacunes (ischemic lesions with a diameter of less than 15 mm); (2) periventricular white matter hyperintensities (WMHs) in T2 weighted images; (3) with or without the presence of microbleeds in susceptibility weighted MR sequences. Exclusion criteria: (1) patients with hereditary vascular disease or a history of hypoxic ischemic encephalopathy, (2) other dementia types, or (3) patients with other organ dysfunction. A total of 106 VD patients were enrolled including 57 males and 49 females with an average age of (61.03±9.12) years old. Another 102 healthy elderly people without dementia who received physical examinations in the same period were selected as controls, including 52 males and 50 females (average age: 60.82±9.78 years). All participants signed the informed consent. This study was approved by the ethnic committee of Armed Police Corps Hospital.

Data collection

Name, age, gender, body mass index (BMI) and disease histories (hypertension, diabetes and hyperlipidemia) were collected from the subjects. Two mL venous blood from the elbow of patients was obtained, and after the plasma was separated, the concentration of homocysteine (Hcy) was measured using the OLYMPUS AU5400 automatic biochemical analyzer and the Hcy detection kit provided by Aosa Pharmaceutical Co., Ltd. The concentrations of folic acid and vitamin B_{12} were determined via the folic acid-CP and vitamin B_{12} analyzers from Siemens.

Deoxyribonucleic acid (DNA) extraction

A total of 1 mL venous blood from the elbow of the patients was drawn to isolate DNA using an extraction kit (Beijing BioTeke Corporation). After that, genotype was detected and analyzed via the TaqMan® single nucleotide polymorphism (SNP) Genotyping Assay kit (Thermo) (**Table 1**).

Statistical analysis

Statistical Product and Service Solutions 20.0 software was adopted for analyzing data. Measurement data were displayed as mean ± standard deviation (SD). Student *t*-test was used for comparison between the two groups. Chi-square test was used for enumeration data. The likelihood ratio chi-square test was applied to analyze the distribution of each genotype. The R×C chi-square test was performed to assess genotype and allele frequency. $P<0.05$ was considered statistically significant.

Results

Comparisons of basic data between two groups

No significant differences were found in age, gender, BMI, hypertension, diabetes and hyperlipidemia between two groups ($P>0.05$) (**Table 2**).

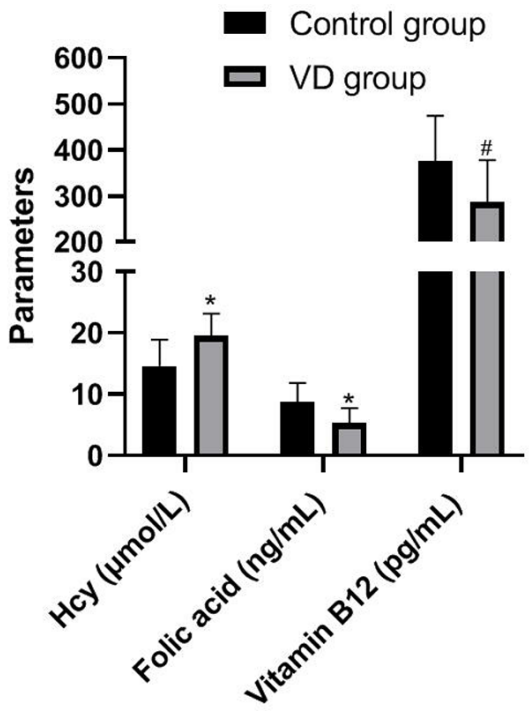

Figure 1. Comparisons of Hcy, folic acid and vitamin B_{12} levels. Compared with control group, *P<0.01; #P<0.05.

Comparisons of Hcy, folic acid and vitamin B_{12} level

Hcy level was significantly decreased while folic acid and vitamin B_{12} levels were statistically elevated in patients from the VD group compared to those in control group (P<0.05) (**Figure 1**).

Genetic equilibrium test

The distributions of PS1 gene rs200165137 genotype frequency in control and VD group were in accordance with the Hardy-Weinberg genetic equilibrium law (P>0.05) (**Table 3**).

Comparison of genotype distribution frequency

The distribution frequencies of genotypes 1/1, 1/2, and 2/2 in the control group were 16.67%, 56.86%, and 26.47%, respectively, while those in the VD group were 36.79%, 44.34% and 18.87%, respectively. The results indicated that the frequency of 1/1 genotype in the VD group was significantly higher than control group (P<0.01), but the frequency of 2/2 genotype in the former was significantly lower than that in the latter (P<0.01) (**Table 4**).

Comparison of allele distribution frequencies

The distribution frequencies of 1 and 2 alleles in the control group were 45.10% and 54.90%, respectively, and in the VD group they were 58.96% and 41.04%, respectively. The frequency of 1 allele in the VD group was significantly increased compared to that in the control group (P<0.01) (OR/95% CI: 0.346/0.279-0.428) (**Figure 2**).

Correlation of PS1 genotypes with Hcy, folic acid and vitamin B_{12} level

There were significant differences of Hcy level among the three rs200165137 genotypes in the PS1 gene in the VD group (P<0.05), namely, 1/1 genotype >1/2 genotype >2/2 genotype. Statistical difference among the three rs200165137 genotypes of Folic acid and vitamin B_{12} level were observed in VD group (P<0.05), namely, 1/1 genotype <1/2 genotype <2/2 genotype (**Table 5**).

Discussion

The pathogenesis of VD manifestes as cerebral arteriosclerosis, stenosis and occlusion leading to insufficient perfusion flow of the brain tissues, brain tissue impairment and reduced brain excitability. It further results in decreased brain metabolism and cerebral blood flow as well as ultimately causes brain cognitive dysfunction. Currently, there are 36 million VD patients worldwide and it has been predicted that the incidence rate of the disease is likely to significantly rise in the next 10 years [6]. Previous evidence has indicated that the high level of Hcy can produce neurocytotoxicity and excitotoxicity in hippocampal neurons, which even causes death of hippocampal neurons. It thus impairs cognitive ability, intellectual ability and memory of patients, and ultimately gives rise to dementia [7-9]. It has been demonstrated that Hcy can function as an indicator for the evaluation of the cognitive function of patients [10]. Consistently, the results of this study verified that the level of Hcy in the VD group was significantly higher than control group. Meanwhile, the metabolism of Hcy requires the involvement of vitamin B_{12}, which is converted to methionine by virtue of methylation. Folic acid acts as a key enzyme that mediates Hcy metabolism and its decreased level can up regulate the level of

Table 3. Detection of the genetic equilibrium of PS1 gene rs200165137 genotypes

Group	n	1/1		1/2		2/2		x^2	*p*
		Actual frequency	Theoretical frequency	Actual frequency	Theoretical frequency	Actual frequency	Theoretical frequency		
Control group	102	17	20.75	58	50.51	27	30.75	2.24	0.33
VD group	106	39	36.85	47	51.30	20	17.85	0.74	0.69

Table 4. Comparisons of rs200165137 genotypes in the PS1 gene [n (%)]

Genotype	Control group	VD group	Odds ratio (OR) [95% confidence interval (95% CI)]	*p*
1/1	17 (16.67)	39 (36.79)		
1/2	58 (56.86)	47 (44.34)	0.333 (0.256-0.434)	0.000
2/2	27 (26.47)	20 (18.87)	0.463 (0.365-0.586)	0.000

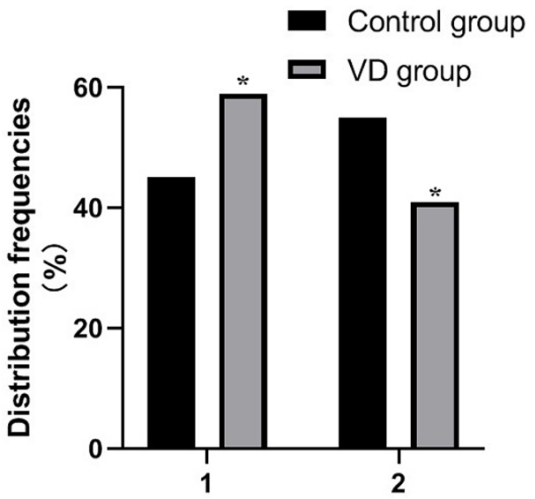

Figure 2. Comparison of rs200165137 allele distribution in the PS1 gene between the two groups (%). Compared with control group, *P<0.01.

Hcy [11]. The deficiency of folic acid and vitamin B_{12} leads to metabolic disorder of Hcy and the occurrence of high Hcy hyperlipidemia. Our study showed significantly higher Hcy and lower folic acid and vitamin B_{12} level in the VD group than control group, indicating that low levels of folic acid and vitamin B_{12} can cause high Hcy hyperlipidemia. Our result was in line with previous evidence which showed that the high level of Hcy and the incidence rate of cerebrovascular disease of patients can be effectively reduced through supplementing folic acid and vitamin B_{12} [12].

As genetic testing techniques develop, researchers have realized that the pathogenesis of VD is implicated to genetic factors in addition to vascular damage. Synergies between mutations in genes such as notch 3, advanced programming 8 and arylsulfatase A-pseudo deficiency and other factors participate in the molecular mechanism of VD [13-15]. Located at 14q24.3, the PS1 gene exhibits high expression in the CNS [16], and it is associated with embryonic development, regulation of intracellular Ca^{2+} concentration, signal transmission and the release of neurotransmitters [17-19]. Mutations in the PS1 gene result in instability of the β-chain protein and damage nerve cells [20]. PS1 gene polymorphism has been reported to have a correlation with the pathogenesis of dementia [21]. In this study, the polymorphism rs200165137 in the PS1 gene was examined, which showed that the frequency of 1/1 genotype in the VD group was significantly higher than control group, but 2/2 genotype in the former was significantly lower than that in the latter. Besides, the frequency of 1 allele in the VD group was higher compared to control. Therefore, it is speculated that the onset of VD is associated with 1/1 genotype and 1 allele of rs200165137 in the PS1 gene. Mutations of the PS1 gene might influence the development of embryos, intracellular Ca^{2+} concentration, signal transmission and the release of neurotransmitters, thereby leading to VD, but the exact mechanism still needs further research.

It was further found that there were significant differences regarding the three genotypes among Hcy, folic acid and vitamin B_{12} levels, namely, Hcy level: 1/1 genotype >1/2 genotype >2/2 genotype and folic acid and vitamin B_{12} levels: 1/1 genotype <1/2 genotype <2/2 genotype. The above results indicate that rs200165137 mutations in the PS1 gene can affect the expression and transport of these molecules, and increase Hcy but decrease

Table 5. Correlation analyses of rs200165137 genotypes in the PS1 gene with the levels of Hcy, folic acid and vitamin B_{12} in the VD group

Item	1/1	1/2	2/2	X^2	*p*
Hcy (μmol/L)	21.53±3.54	20.12±3.12	18.73±4.57	2.665	0.046
Folic acid (ng/mL)	4.67±1.34	5.01±2.21	5.51±2.78	2.868	0.043
Vitamin B_{12} (pg/mL)	266.53±90.98	282.22±90.77	268.23±91.67	3.354	0.032

folic acid and vitamin B_{12} level. However, limitations in this study still exists in that the exact mechanism concerning how PS1 gene mutations affect Hcy levels remains unclear, and requires further elucidation.

Conclusion

In conclusion, the onset of VD has a correlation with the 1/1 genotype of rs200165137 in the PS1 gene and the gene carrying 1 allele can increase the risk of VD.

Disclosure of conflict of interest

None.

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