TNF-α (G308A) Polymorphism and Vascular Parkinson Complicated with Pulmonary Infection

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ABSTRACT
Objective: To analyse relationship between tumour necrosis factor-α (TNF-α) (G308A) polymorphism and Vascular Parkinson (VP) complicated with pulmonary infection.

Study Design: Analytical study.

Place and Duration of Study: Zhuji people's Hospital, China, from February 2017 to April 2021.

Methodology: Eighty five patients with VP complicated with pulmonary infection were included in the observation group. Eighty five patients with VP were included in the comparison group. Genotypic analysis of TNF-α (G308A) and serum TNF-α were detected.

Results: TNF-α (G308A) polymorphism in both the observation group and control group conformed to the genetic balance rule by the Hardy-Weinberg test. The frequency of each gene satisfied the genetic balance (p=0.175, and p=0.184, respectively). Geno-type distribution and alleles of TNF-α (G308A) between the observation group and the control group were different (both p <0.001). Compared with control group, serum TNF-α level in the observation group was higher (p <0.001). In the observation group, serum TNF-α level in cases with GA+AA genotype (carrying A allele) was higher than that in cases with GG genotype (non A allele) (p <0.001).

Conclusion: TNF-α (G308A) polymorphism is associated with VP complicated with pulmonary infection. VP Patients with TNF-α (G308A) AA genotype and an allele may have a high risk of pulmonary infection.

Key Words: Tumor necrosis factor-α (TNF-α), Polymorphism, Vascular Parkinson (VP), Pulmonary infection.

INTRODUCTION
Vascular Parkinson's (VP) is a disease with clinical manifestations similar to Parkinson's disease (PD) caused by ischemic cerebrovascular disease or arteriosclerosis.1 VP occurs insidiously and patients often have a history of recurrent stroke, hypertension, and/or diabetes. VP patients are prone to complicate pulmonary infection because of dysphagia, decreased immunity, and other factors.2 VP complicated with pulmonary infection is easy to cause hypoxia, which can induce central nervous system dysfunction and multiple organ failure. However, most patients with VP complicated with pulmonary infection lack typical clinical manifestations and are easy to be ignored. The pathogenesis of VP complicated with pulmonary infection is complexed, involving many systems including immunity, neurology, and so on, and its specific mechanism has not yet been fully clarified.

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Tumor necrosis factor-α (TNF-α) can be significantly increased in acute infection.3 TNF-α gene G308A is a promoter of TNF-α gene.4 Among them, AA and AG genotypes are called TNF-α high yield type, and cells carrying AA and AG genotypes can secrete more TNF-α. Some studies have shown that the polymorphism of TNF-α gene promoter may be a risk factor of pneumonia and severe pneumonia, and may increase the mortality in patients with severe pneumonia.5 TNF-α (G308A) polymorphism is associated with pulmonary infection after cerebral infarction.6 Studies have reported that TNF-α gene polymorphism at position -308 in the promoter region may not be a predisposing factor of hospital-acquired pneumonia, but it may affect the incidence and prognosis of severe hospital-acquired pneumonia by affecting the level of TNF-α.7 TNF-α (G308A) polymorphism is associated with influenza pneumonia complications.8 Whether a relationship exists between TNF-α (G308A) polymorphism and VP complicated with pulmonary infection is not clear now.

The objective of this study was to assess whether there was an association exists between TNF-α (G308A) polymorphism and VP complicated with pulmonary infection.
**METHODOLOGY**

This analytical study was conducted at Zhuji Hospital of traditional Chinese medicine, Zhejiang, China. A total of 85 cases with VP complicated with pulmonary infection admitted to our Hospital from February 2017 to April 2021 were included in an observation group. In observation group, 43 (50.59 %) were males and 42 (49.41%) were females. Inclusion criteria of the observation group were that cases met diagnostic criteria of VP and pulmonary infection; X-ray or CT showed pulmonary infection; and no immunodeficiency disease. Exclusion criteria were that patients complicated with other infected diseases; with renal dysfunction; with benign and malignant tumor diseases; and with PD caused by drugs, trauma and other causes. Meanwhile, 85 patients with VP admitted to our hospital in the corresponding period were included in a control group. In the control group, 44 (51.76%) were males and 41(48.24%) were females. Inclusion criteria of the control group were that cases met the diagnostic criteria of VP; no symptoms of infection or infectious diseases at admission. Exclusion criteria were that cases complicated with renal dysfunction, benign and malignant tumors, and PD caused by drugs, trauma and other reasons.

According to the new diagnostic criteria proposed by Zijlmans et al. and Winikates et al., the patients in the observation group and the control group excluded Parkinson-plus syndrome, and with informed consent signed by the patients or their families.

Two mL venous blood was collected fast after admission. The genotypic analysis of TNF-α (G308A) was carried out by polymerase chain reaction (PCR). Extraction of genomic DNA from blood was used by a genomic DNA rapid extraction kit. The extracted DNA was stored at -20℃. Referring to the methods of Sakao et al. and Wang et al., primers of G308A genotype of TNF-α gene were designed. Upstream primer was 5'-AGG CAATAG GTTTTG AGG GCCAT-3' and downstream primer was 5'-GAG CGTCTG CTGGCT GGG TG-3'. The PCR reaction products were purified and sequenced by reverse sequencing. The genotype of TNF-α gene was determined according to the sequencing results, namely, the wild type base G single peak suggested homozygous mutant (GG) genotype; the heterozygous GA double peak suggested heterozygote (GA) genotype; and the homozygous base a single peak suggested normal wild type (AA) genotype.

At the same time, 2mL fasting venous blood was collected in the morning after admission, and the serum TNF-α level was measured by ELISA method.

Data analysis was performed using SPSS version 25.0. The normality of variables was assessed by Kolmogorov-Smirnov or Shapiro-Wilk test. Measurement data followed a normal distribution were expressed in mean ± SD, and independent sample t-test was used to perform between-group comparisons. Counting data were expressed in n (%). Chi-square test was performed to examine the Hardy-Weinberg genetic balance and compare genotypes and allele frequencies between groups. A p <0.05 was considered statistically significant.

**RESULTS**

Gender, age, history of hypertension, history of diabetes, history of coronary heart disease, and frequency of cerebral infarction between the two groups were not different (p=0.878, 0.535, 0.283, 0.439, 0.362, and 0.293 respectively, Table I).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observation group (n=85)</th>
<th>Control group (n=85)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>43(50.59)</td>
<td>44(51.76)</td>
<td>0.878</td>
</tr>
<tr>
<td>Female [n (%)]</td>
<td>42(49.41)</td>
<td>41(48.24)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes [n (%)]</td>
<td>69.96±9.94</td>
<td>69.01±10.03</td>
<td>0.535</td>
</tr>
<tr>
<td>No [n (%)]</td>
<td>30.04±10.03</td>
<td>30.99±9.96</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes [n (%)]</td>
<td>47(55.29)</td>
<td>40(47.06)</td>
<td>0.283</td>
</tr>
<tr>
<td>No [n (%)]</td>
<td>38(44.71)</td>
<td>45(52.94)</td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes [n (%)]</td>
<td>39(45.88)</td>
<td>34(40.00)</td>
<td>0.439</td>
</tr>
<tr>
<td>No [n (%)]</td>
<td>46(54.12)</td>
<td>51(60.00)</td>
<td></td>
</tr>
<tr>
<td>History of coronary heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes [n (%)]</td>
<td>22(25.88)</td>
<td>17(20.00)</td>
<td>0.362</td>
</tr>
<tr>
<td>No [n (%)]</td>
<td>63 (74.12)</td>
<td>68(80.00)</td>
<td></td>
</tr>
<tr>
<td>Frequency of cerebral infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One [n (%)]</td>
<td>66(77.65)</td>
<td>60(70.59)</td>
<td>0.293</td>
</tr>
<tr>
<td>Greater than or equal to 2 [n (%)]</td>
<td>19(22.35)</td>
<td>25(29.41)</td>
<td></td>
</tr>
</tbody>
</table>

The TNF-α (G308A) gene polymorphism in both the observation group and the control group conformed to the genetic balance rule by the Hardy-Weinberg test, and the frequency of each gene satisfied the genetic balance (p=0.175, p=0.184, respectively).

Genotype distribution and alleles of TNF-α (G308A) between the observation group and control group were different (both p <0.001, Table II).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observation group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum TNF-α level (pg/mL)</td>
<td>8.00±0.72</td>
<td>7.04±0.6</td>
<td></td>
</tr>
<tr>
<td>History of coronary heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes [n (%)]</td>
<td>22(25.88)</td>
<td>17(20.00)</td>
<td></td>
</tr>
<tr>
<td>No [n (%)]</td>
<td>63(74.12)</td>
<td>68(80.00)</td>
<td></td>
</tr>
</tbody>
</table>
| Gender, age, history of hypertension, history of diabetes, history of coronary heart disease, and frequency of cerebral infarction between the two groups were not different (p=0.878, 0.535, 0.283, 0.439, 0.362, and 0.293 respectively, Table I).

In the observation group, serum TNF-α level in 60 cases with GA+AA genotype (carrying A allele) was 8.32±0.56 (pg/mL), which is higher than that in 25 cases with GG genotype (non A allele) 7.24±0.42 (pg/mL, p <0.001).

**DISCUSSION**

TNF-α has the function of inducing inflammation and immunomodulatory. TNF-α 308 is considered to be the most important gene site affecting the expression of TNF-α gene in vivo. Hardy-Weinberg genetic equilibrium law is the basic law of population genetics. In this study, the polymorphism of TNF-α (G308A) gene in the two groups conformed to the genetic balance rule by the Hardy-Weinberg test, which indicated that the research samples of the observation group and the control group had good genetic representativeness.

The occurrence and development of autoimmune diseases were associated with genotype A of TNF-α 308. It has been found that TNF-α 308 G/A polymorphism is a risk factor for COPD.
This study found that there were significant differences in the distribution and alleles of TNF-α (G308A) genotype between the two groups, suggesting that it may be associated with VP complicated with pulmonary infection.

TNF-α is involved in many kinds of physiological reactions including immunity, anti-infection and so on.17 TNF-α gene is an important cytokine with multifunctional function in vivo. Its gene polymorphism is related to the function of TNF-α.18 The polymorphism of the gene promoter region may affect its transcriptional level, and then affect the development and prognosis of the disease. Studies have shown that patients with TNF-α (G308A) genotype and A genotype have a high risk of pulmonary infection in those with cerebral infarction.6

It was found that the level of serum TNF-α in cases with GA+AA genotype (carrying A allele) was higher, comparing with cases with GG genotype (without A allele). The results suggested that cells carrying TNF-α (G308A) genotype AA and AG could secrete more TNF-α. The results of this study are basically consistent with previous studies.19,20 It suggested that TNF-α 308A may be involved in the regulation of mRNA transcription and TNF-α synthesis and secretion in patients with VP complicated with pulmonary infection, which may aggravate the inflammation and pulmonary infection. The number of subjects observed is limited. Further studies with a larger sample size are needed to study the relationship between TNF-α (G308A) polymorphism and susceptibility to VP complicated with pulmonary infection. At the same time, other genes related to VP complicated with pulmonary infection should be studied, in order to reveal the molecular mechanism of its occurrence and development and provide the theoretical foundation for controlling its occurrence.

CONCLUSION

TNF-α (G308A) gene polymorphism is associated with VP complicated with pulmonary infection. VP Patients with TNF-α (G308A) AA genotype and A allele may have a high risk of pulmonary infection.

ETHICAL APPROVAL:

This study was approved by the Research Ethical Committee of the Zhuji people’s Hospital, China.

PATIENTS’ CONSENT:

Informed consent was obtained from all participants.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS’ CONTRIBUTION:

XS: Analysis or interpretation of data for the work, writing, discussion, literature review, and critical revision of the manuscript.

YH: Conception and design, discussion, and literature review.

ZS: Discussion, literature review.

LC: Data analysis, literature search, and discussion.

REFERENCES


