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Effect of VEGF on neurological impairment and prognosis of acute cerebral infarction patients

A retrospective case-control study

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Abstract

Objective: Due to the complex pathological mechanism of acute cerebral infarction, the role of vascular endothelial growth factor (VEGF) on the disease is not clear. Therefore, a retrospective case-control study was performed to explore the effect of VEGF on neurological impairment and prognosis of acute cerebral infarction patients.

Method: A total of 100 patients with acute cerebral infarction admitted to our hospital from April 2021 to April 2022 were selected. Blood samples from all patients would be routinely collected to detect the expression of serum VEGF. Pearson chi-square, Spearman correlation and univariate Logistic regression were used to analyze the clinical data to explore the relationship between VEGF expression and basic information, stroke degree, quality of life, and prognosis of patients. To determine whether VEGF can provide relevant basis for the early prevention and prognostic treatment of acute cerebral infarction. And multivariate logistic regression was used to calculate the odds ratio between each variable and VEGF expression.

Results: Pearson chi-square test and Spearman correlation coefficient showed that sex, degree of stroke, limb convulsions, loss of consciousness, hemiplegia, aphasia, mental functioning score, overall quality of life score, and short-term prognosis were significantly correlated with VEGF expression in 100 patients. Univariate logistic regression was used to describe the ORs and 95% confidence interval of subjects at the univariate level, and the degree of stroke (OR = 83.333, $P < 0.001$), tic of limbs (OR = 26.316, $P < 0.001$), loss of consciousness (OR = 23.256, $P < 0.001$), hemiplegia (OR = 62.500, $P < 0.001$), aphasia (OR = 76.923, $P < 0.001$), mental functioning score (OR = 7.937, $P < 0.001$), overall quality of life score (OR = 5.464, $P < 0.001$), short-term prognosis (OR = 37.037, $P < 0.001$) was significantly correlated with the high expression of VEGF.

Conclusions: The level of serum VEGF was positively correlated with neurological impairment degree and prognosis in patients with acute cerebral infarction, the more severe the degree of stroke and the worse the prognosis.

Abbreviations: CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, HIF-1 = hypoxia-inducible factor 1, NIHSS = National Institutes of Health Stroke Scale, OR = odds ratio, VEGF = vascular endothelial growth factor.

Keywords: acute cerebral infarction, neurological deficit, prognosis, stroke, vascular endothelial growth factor

1. Introduction

Acute cerebral infarction is a common disease with high disability and mortality. Due to the complex pathological mechanism of the disease, there is still a lack of effective early diagnosis and disease prediction methods.[1,2] Growth factor is an important regulator of cerebral ischemia protection and recovery, among which vascular endothelial growth factor (VEGF) plays an important role in angiogenesis and neuroprotection.[3] However, the role of VEGF on the disease is not clear.

One study found that increased VEGF-A levels may be used as A predictor of improved recovery from cerebral infarction.[4] However, under pathological conditions, the disease was aggravated by the destruction of the blood-brain barrier mediated by VEGF and neuroinflammatory reaction. Studies have shown that VEGF-A level is positively correlated with the severity of stroke in cardiovascular embolic infarction, while VEGF-A level is negatively correlated with the severity of nervous system in atherosclerotic thrombotic infarction.[5] Therefore, it is difficult to determine when VEGF is beneficial.[6,7]

This study aimed to investigate the correlation between serum VEGF level and the degree and prognosis of early neurological impairment in patients with acute cerebral infarction, so as to

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The authors have no conflict of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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provide guidance for the early diagnosis and prognosis of acute cerebral infarction.

2. Materials and Methods

2.1. Details of study design

This research was a retrospective case-control study.

2.2. Setting

Acute cerebral infarction was a serious disease, which affected people's health. The role of VEGF on the disease is not clear.

2.3. Sample size estimation

$$n = \frac{z^2}{d^2}\sigma^2$$

Z is the confidence interval, n was the sample size, d is the sampling error range, and σ was the standard deviation, which is generally 0.5.

2.4. Sampling technique

Stratified random sampling was used. The stratified random sampling method was to first divide the units of the population into several types according to a certain standard, and then determined the number of sample units from each type according to the ratio of the number of type units to the number of overall units, and finally select the number of sample units from each type according to the random principle. Take a sample. Stratified random sampling is characterized by stratifying first and then randomly sampling within each stratum.

2.5. Participant

A total of 100 patients with acute cerebral infarction and related staff admitted to our hospital from April 2021 to April 2022 were enrolled in this study. Routine blood sampling was performed for these patients to detect the expression of VEGF in their serum, and the clinical data were collected and analyzed. By analyzing these clinical data, we found the relationship between VEGF expression and patients' basic information, stroke degree, quality of life, and prognosis.

$$n = \frac{z^2}{d^2}\sigma^2$$

Inclusion criteria: 18–100 years old; patients with acute cerebral infarction; all patients were confirmed by neurological examination and head CT diagnosis, and were complicated with varying degrees of neurological dysfunction; no intracranial or extracranial infection.

Exclusion criteria: <18 years old or >100 years old; Exclude the occurrence of infected persons; With other serious primary diseases; Accompanied by severe primary mental disorders and obvious cases of noncooperation.

2.6. Primary and secondary outcome variables with working definition

Primary outcome variables: the expression of serum VEGF, the degree of stroke and the prognosis.

Secondary outcome variables: the tic of limbs, loss of consciousness, hemiplegia, aphasia, mental functioning score, overall quality of life score, short-term prognosis

2.7. Intervention/issue of interest and comparison

Enzyme-linked immunosorbent assay (ELISA) detection of VEGF was performed. And the expression of VEGF was defined as the intervention/issue of interest and comparison. The reagent was human VEGF ELISA kit (Wuhan Sanying Company, KE00085). Carry out the experiment procedure according to the instruction. Processing samples to prepare standard, add sample (standard and sample), wash plate, add detection antibody solution, incubate, wash plate, add enzyme solution, incubate, wash plate, add TMB substrate, add stop solution 50 μl, immediately 450 nm reading (double antibody sandwich method), calculate the VEGF content in the sample by standard curve. We took the mean VEGF concentration as the boundary. VEGF concentration < 125 pg/mL was defined as low, and VEGF concentration ≥125 pg/mL was defined as high.

2.8. Assessment of stroke severity and short-term prognosis

National Institutes of Health Stroke Scale (NIHSS) was used to evaluate the neurological deficits of patients on admission, and the observation group was divided into mild, moderate and severe stroke groups according to NIHSS score. Spearman correlation analysis was performed to compare the correlation between serum VEGF levels and prognostic indicators of patients.

The NIHSS score of the observation group was reevaluated on the 14th day of onset to judge the short-term prognosis, and the patients were divided into the good prognosis group and the poor prognosis group. The predictive value of VEGF in the short-term prognosis of patients with acute cerebral infarction was evaluated by using the receiver operating characteristic curve.

2.9. Ethics, informed consent, and the end point

This study was approved by the Ethics Committee of Cangzhou Central Hospital (2016CZH75, March 20, 2016). All patients received written informed consent.

2.10. Statistical analysis

The data were expressed as a percentage of the total. Pearson chi-square test was used to analyze the relationship between clinical parameters and VEGF expression. Spearman test was used to compare the correlation between clinical data and VEGF expression level. Univariate logistic regression analysis and multivariate logistic regression were used to calculate the odds ratio between each variable and VEGF expression. Statistical analysis was performed using SPSS 21.0 (IBM, Armonk, NY). $P<0.05$ was considered statistically significant.

3. Results

3.1. Baseline information of the patients

There were 58 male patients and 42 female patients in the study. And the all participants included 48 cases with the age ≤ 60 years old and 52 cases with the age >60 years old (Table 1).

3.2. Primary outcome variables

A total of 61 individuals were with low expression of VEGF, and 39 patients were with the high expression of VEGF. There was a total of 41 patients with mild degree of stroke, 13 patients with moderate degree of stroke, 46 patients with severe degree

Table 1

VEGF expression and general characteristics of patients.

Clinical features		VEGF Low (%)	VEGF High (%)	*P*
Sex				0.006*
Male	58	42 (72.4%)	16 (27.6%)	
Female	42	19 (45.2%)	23 (54.8%)	
Age				0.599
≤60	48	28 (58.3%)	20 (41.7%)	
>60	52	33 (63.5%)	19 (36.5%)	
The degree of stroke				0.001*
mild	41	6 (14.6%)	35 (85.4%)	
moderate	13	9 (69.2%)	4 (30.8%)	
severe	46	46 (100%)	0 (0%)	
Tic of limbs				0.001*
Yes	41	9 (22.0%)	32 (78.0%)	
No	59	52 (88.1%)	7 (11.9%)	
Loss of consciousness				0.001*
Yes	42	10 (23.8%)	32 (76.2%)	
No	58	51 (87.9%)	7 (12.1%)	
Hemiplegia				0.001*
Yes	40	6 (15.0%)	34 (85.0%)	
No	60	55 (91.7%)	5 (8.3%)	
Aphasia				0.001*
Yes	39	5 (12.8%)	34 (87.2%)	
No	61	56 (91.8%)	5 (8.2%)	
Mental functioning ggjjscore mental functioning score mental functioning score mental functioning score score				0.001*
≤20	48	18 (37.5%)	30 (62.5%)	
>20	52	43 (82.7%)	9 (23.1%)	
Overall quality of life score				0.001*
≤70	40	15 (37.5%)	25 (62.5%)	
>70	60	46 (76.7%)	14 (23.3%)	
Short-term prognosis				
Bad	41	8 (19.5%)	33 (80.5%)	0.001*
Good	59	53 (89.8%)	6 (10.2%)	

Pearson chi-square test. VEGF = vascular endothelial growth factor.
*$P < 0.05$.

of stroke. A total of 41 patients had the bad prognosis and 59 patients had the good prognosis (Table 1).

3.3. The neurological impairment and prognosis based on Chi-square test are closely related to VEGF

Pearson chi-square test showed that the expression of VEGF was related with the neurological impairment and prognosis of acute cerebral infarction patients. In patients, sex ($P = .006$), the degree of stroke ($P < 0.001$), tic of limbs ($P < 0.001$), loss of consciousness ($P < 0.001$), hemiplegia ($P < 0.001$), aphasia ($P < 0.001$), Mental functioning score ($P < 0.001$), overall quality of life score ($P < 0.001$), short-term prognosis ($P < 0.001$) were significantly correlated with VEGF expression. There was no significant difference between age and VEGF expression ($P = .599$) (Table 1).

3.4. Spearman test was used to further analyze the correlation between neurological impairment and prognosis and VEGF.

Spearman test was used to further confirm whether relevant clinical features play an important role in VEGF. Spearman correlation coefficient showed VEGF and sex ($\rho = 0.275$, $P = .006$), the degree of stroke ($\rho = 0.812$, $P < 0.001$), tic of limbs ($\rho = 0.667$, $P < 0.001$), loss of consciousness ($\rho = 0.649$, $P < 0.001$), hemiplegia ($\rho = -0.770$, $P < 0.001$), aphasia ($\rho = 0.790$, $P < 0.001$), mental functioning score ($\rho = 0.463$, $P < 0.001$), overall quality of life score ($\rho = 0.393$, $P < 0.001$) and short-term prognosis ($\rho = 0.709$, $P < 0.001$) were statistically significant. There was no significant correlation between VEGF and age ($\rho = -0.053$, $P = .604$) (Table 2).

Table 2

Correlation analysis of VEGF expression and general characteristics of patients.

Clinical features	VEGF ρ	VEGF *P*
Sex	0.275	0.006*
Age	–0.053	0.604
The degree of stroke	0.812	<0.001*
Tic of limbs	0.667	<0.001*
Loss of consciousness	0.649	<0.001*
Hemiplegia	0.770	<0.001*
Aphasia	0.790	<0.001*
Mental functioning score	0.463	<0.001*
Overall quality of life score	0.393	<0.001*
Short-term prognosis	0.709	<0.001*

Spearman correlation test. VEGF = vascular endothelial growth factor.
*$P < 0.05$.

3.5. The effect of VEGF expression on neurological impairment and prognosis by univariate logistic regression

Univariate logistic regression was used to describe the ORs and 95%CI of the subjects at the univariate level, and the degree of stroke was obtained (OR = 83.333, $P < 0.001$), tic of limbs (OR = 26.316, $P < 0.001$), loss of consciousness (OR = 23.256, $P < 0.001$), hemiplegia (OR = 62.500, $P < 0.001$), aphasia (OR = 76.923, $P < 0.001$), mental functioning score (OR = 7.937, $P < 0.001$), overall score of quality of life (OR = 5.464, $P < 0.001$), short-term prognosis (OR = 37.037, $P < 0.001$) was significantly correlated with the high expression of VEGF (Table 3).

3.6. The effect of VEGF on neurological impairment and prognosis by multivariate logistic regression

Multivariate logistic regression was used to describe the ORs and 95%CI of the subjects at the univariate level, and the degree of stroke was obtained (OR = 2.158, $P = 0.041$), tic of limbs (OR = 1.631, $P = 0.006$), loss of consciousness (OR = 1.542, $P = 0.005$), hemiplegia (OR = 1.740, $P = 0.050$), aphasia (OR = 10.266, $P << 0.001$), mental functioning score (OR = 2.020, $P = 0.011$), overall score of quality of life (OR = 1.242, $P = 0.032$), short-term prognosis (OR = 1.254, $P = 0.048$) was significantly correlated with the high expression of VEGF (Table 4).

4. Discussion

Main findings of the present study showed that degree of stroke, limb convulsions, loss of consciousness, hemiplegia, aphasia, mental functioning score, overall quality of life score, and short-term prognosis were significantly correlated with VEGF expression in acute cerebral infarction patients. The severity of stroke in patients with 14 days of cerebral infarction was positively correlated with VEGF, and the short-term prognosis was positively correlated with VEGF expression level.

Comparison with other studies, and implication and explanation of findings were discussed in the followed paragraphs. Cerebral ischemia can lead to focal hypoxia or ischemia.

Table 3

Risk assessment of VEGF expression on patients' prognostic symptoms by Logistic regression analysis.

		VEGF		
Clinical features		**Low**		**High**
The degree of stroke	OR	1		83.333
	P		0.001*	
Tic of limbs	OR	1		26.316
	P		0.001*	
Loss of consciousness	OR	1		23.256
	P		0.001*	
Hemiplegia	OR	1		62.500
	P		0.001*	
Aphasia	OR	1		76.923
	P		0.001*	
Mental functioning score	OR	1		7.937
	P		0.001*	
Overall quality of life score	OR	1		5.464
	P		0.001*	
Short-term prognosis	OR	1		37.037
	P		0.001*	

OR = Odds Ratio, 95% CI = 95% confidence interval, VEGF = vascular endothelial growth factor.
* $P < 0.05$.

Table 4

Risk assessment of VEGF expression on patients' prognostic symptoms by multivariate Logistic regression analysis.

	VEGF		
Characteristics	**OR**	**95%CI**	**P**
The degree of stroke	2.158	0.787–5.915	0.041
Tic of limbs	1.631	0.242–1.645	0.006
Loss of consciousness	1.542	0.577–4.272	0.005
Hemiplegia	1.740	0.268–2.041	0.050
Aphasia	10.266	3.866–27.264	<0.001*
Mental functioning score	2.020	0.747–5.460	0.011
Overall quality of life score	1.242	0.965–1.365	0.032
Short-term prognosis	1.254	0.874–1.693	0.048

OR = odds ratio, 95% CI = 95% confidence interval, VEGF = vascular endothelial growth factor.
* $P < 0.05$.

Growth factors are closely related to recovery after cerebral ischemia. VEGF-A is a key regulator of angiogenesis, neuroprotection, and neurogenesis. However, excessive VEGF-A in the early stage of stroke can also lead to leakage of the blood-brain barrier in ischemic brain, resulting in edema. Subsequently, increased intracranial pressure obstructs blood supply and aggravates nerve injury.[8,9] Therefore, the timing, dose, and route of VEGF-A administration after stroke all have an impact on prognosis. Studies have shown that VEGF-A should not be administered intravenously within 24 hours of stroke. One day after stroke, VEGF-A can play a neuroprotective role. At this time, a large amount of VEGF-A can increase vascular capacity, reduce the lesion volume, enhance nerve cell proliferation, and even improve the behavior recovery after stroke.[10–12]

VEGF-A and its receptors, VEGFR-1 and VEGFR-2, are upregulated in stroke response.[10]This increase occurred mainly in the penumbra. If sufficient perfusion can be restored in time, the penumbra cells can be saved. In animal models of cerebral ischemia, use of VEGF-A or drugs that enhance VEGF-A can reduce lesion volume.[13] VEGF-A and VEGF receptors have been reported to increase as early as 2-4 hours after stroke onset and persist for at least 28 days.[14,15] VEGF-A increases bidirectionally during ischemia. Studies have shown that VEGF-A shows its first peak at 6 hours after cerebral ischemia, returns to normal within 12 hours, and reaches its peak again at 7 days after cerebral ischemia.[16,17] Studies have shown that hypoxia-inducible factor 1 (HIF-1) is a key transcription factor in cerebral infarction. HIF-1α is A significant activator of VEGF-A gene expression.[18] Meanwhile, HIF-1α induces erythropoietin, which in turn increases VEGF secretion.[19,20] Inflammatory cytokines also regulate VEGF-A in stroke.[21,22]

Increased VEGF-A levels were also associated with increased collateral formation,[23] reducing the degree of stroke ischemia. In addition, distal ischemic preconditioning can also protect organs from ischemic injury by increasing VEGF-A levels throughout the body. Clinical trials have shown that ischemic preconditioning is feasible in people at high risk of stroke and significantly reduces the incidence of stroke.[24,25]

Many previous literatures have discussed the clinical application of VEGF in cerebral ischemia, but the data supporting the protective effect of VEGF-A are almost entirely based on animal models, and there are few clinical studies, mainly focusing on the increased level of human serum VEGF-A after stroke. However, how the level of VEGF-A is related to the severity of stroke remains to be clarified.

This study analyzed the correlation between serum VEGF expression level and the degree of stroke and prognosis in patients with acute cerebral infarction. The degree of stroke in patients with acute cerebral infarction was positively correlated with VEGF. The higher the expression level of VEGF, the more severe the degree of stroke and the worse the prognosis.

4.1. Strengths and limitations

Our study provides powerful biochemical evidence for predicting the condition and prognosis of patients with acute cerebral infarction, and provides reference for guiding clinical treatment.

At present, there are few studies on the correlation between serum VEGF and severity of acute cerebral infarction. To study the dynamic changes of serum VEGF levels in patients with acute cerebral infarction is helpful for the early diagnosis of acute cerebral infarction. In this study, serum VEGF in patients with acute cerebral infarction was combined with the degree of neurological impairment to explore more effective indicators for clinical practice. However, there were some limitations in the study. First, this study was a single-center clinical analysis, and the number of cases obtained was limited. Second, we did not thoroughly explore the potential molecular mechanism of VEGF in acute cerebral infarction.

5. Conclusions

The expression of serum VEGF in patients with acute cerebral infarction is closely related to neurological impairment and prognosis. The level of serum VEGF was positively correlated with neurological impairment degree and prognosis in patients with acute cerebral infarction.

6. Recommendation and Future directions

Acute cerebral infarction, as a disease with high mortality and difficult to cure, seriously threatens people's health and life safety, and brings heavy burden to individuals and the country. Once acute cerebral infarction occurs, a series of continuous physiological and pathological reactions occur in the body. Therefore, improving the cure rate of cerebral infarction will be our main task in the future. Through the analysis of the effect of VEGF on acute cerebral infarction, it is not difficult to find that in order to effectively prevent the occurrence of acute cerebral infarction, it is necessary to comprehensively start from serum factor. Fundamentally improving the prognosis and life quality were the ultimate goal of treatment. In the future, we will conduct a multi-center randomized controlled clinical study and

further expand the sample size to analyze the effect of VEGF on acute cerebral infarction.

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