Revista Argentina de Clínica Psicológica
2020, Vol. XXIX, N°5, 50-56
DOI: 10.24205/03276716.2020.1006

To Explore the Expression of ANGPTL4 in Patients with Acute Cerebral Infarction and Its Relationship with Carotid Atherosclerosis

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Abstract

Objective- To investigate the expression of ANGPTL4 in patients with acute cerebral infarction (acute cerebral infarction) and its relationship with carotid atherosclerosis.

Methods- A total of 60 ACI patients who were admitted to this hospital from May 2015 to February 2017 were selected as the observation group, and 60 healthy individuals who underwent physical examination were selected as substitutes. The ANGPTL4 expression level was detected and compared by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) when the inserted subjects were admitted; at the same time, the biochemical indicators of the target subjects included TG, SOD, TC, HDL-C, LDL-C, FPG, FINS, TNF-α levels were detected and compared; and the relevant indicators of carotid atherosclerosis of the research subjects were measured mainly including carotid intima-media thickness (CIMI) and the largest area of plaque, and carotid artery was measured Atherosclerosis hardener and compare. After comparison, the correlation between the ANGPTL4 level and other indicators were studied, and the multi-element regression analysis of the factors affecting the serum IMT level was performed. Finally, the multi-factor regression analysis of the carotid atherosclerosis in ACI patients was performed.

Results- According to classification, the expression level of ANGPTL4 in the serum of patients in the observation group was significantly reduced (P <0.05); compared with subdivision, the levels of TG and SOD in the observation group were significantly reduced (P <0.05); and in the classification, the levels of TC, HDL-C, LDL-C, FPG, FINS, and TNF-α in the observation group were significantly increased (P <0.05); the carotid atherosclerosis area and Crouse score of the alternative study subjects were all significant increased (P <0.05); According to human analysis, the expression level of ANGPTL4 was positively correlated with TG and SOD levels (P <0.05), but negatively correlated with LDL-C, FPG, FINS, CIMT, the largest plaque area and the crossover level Correlation (P <0.05); the multivariate regression analysis of CIMT showed that ANGPTL4 and TNF-α are independent influencing factors of patients with CIMT; the multivariate regression analysis of carotid atherosclerosis in patients with ACI found that age, smoking History, hypertension and ANGPTL4 level are factors that affect carotid atherosclerosis (P <0.05).

Complications- The expression of ANGPTL4 is down-regulated in ACI patients. ANGPTL4 can protect ACI patients by stabilizing carotid atherosclerosis and inhibiting carotid atherosclerosis.

Keywords- ANGPTL4; acute cerebral infarction; expression; carotid atherosclerosis; correlation

Acute cerebral infarction (Acute cerebral infarction, ACI) refers to brain tissue necrosis caused by sudden interruption of blood supply to the brain [1]. It occurs mostly in the elderly. The main clinical manifestations are headache, dizziness, tinnitus, and hemiplegia [2]. According to relevant research [3], ACI is the global cause of death and disability among adults. Among them, atherosclerosis is the main cause of disease. The mechanism is that the unstable atherosclerotic

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plaque will rupture after being eroded, so that the platelets in the blood stream will be activated, and the activated platelets can make the leukocytes in the blood stream attach to the vascular endothelial injury. Leukocytes will release inflammatory mediators, which will further aggravate the damage of endothelial cells and release platelet activating factor. The activation factor can promote the aggregation of inflammatory factors and the activation of platelets; such repeated cycles will eventually cause ischemic diseases [4]. For the treatment of ACI, clinically, thrombolytic therapy is mainly used to improve the blood circulation of patients with cerebral ischemia and promote the recovery of nerve function [5]. Due to the limitation of the treatment time window of ACI, judging the severity of the patient's condition at an early stage can give him a reasonable treatment method to save the patient's life. Angiopoietin-like protein (Angiopoietin-like protein) is a gene locus related to lipid metabolism. It is secreted by visceral fat cells. Its structure is similar to that of angiopoietin. It has the functions of regulating angiogenesis, improving the survival of hematopoietic cells and repairing [6]. According to foreign studies [7], ANGPTL4 has a promoting effect on blood vessel production and plays an important role in glucose and lipid metabolism. Therefore, it is inferred that it may be closely related to the occurrence and progression of atherosclerosis. This article will study the expression of ANGPTL4 in patients with acute cerebral infarction and its relationship with carotid atherosclerosis, aiming to provide clinical reference and suggestions for the treatment timing of ACI. The report is as follows.

1. Materials and methods

1.1 General information

A total of 60 ACI patients admitted to our hospital from May 2015 to February 2017 were selected, including 35 males and 25 females, aged 42-75 years, with an average age of 60.48±8.59 years old. The course of the disease was 2-8 days, and the average area of the largest cranial plane was 3.01±0.49cm2. Among them, there were 30 cases of smoking history, 20 cases of drinking history, 45 cases of diabetes, 20 cases of coronary heart disease, 35 cases of hypertension, and 23 cases of hyperlipidemia. In addition, healthy people who underwent physical examination during the same period were selected as the control group. All the research subjects and their families were aware of this study and had signed an informed consent form.

1.2 Inclusion criteria and exclusion criteria

Inclusion criteria: (1) Those with complete clinical data; (2) Those who can cooperate with this study; (3) Women who are not pregnant or breastfeeding; (4) Cerebral infarction is diagnosed by head CT or head magnetic resonance (MRI) ; (5) The patient is between 42 and 75 years old. Exclusion criteria: (1) Patients with severe liver and kidney dysfunction; (2) Transient ischemic attack; (3) Cerebral hemorrhage, brain tumor, brain trauma; (4) Family history of mental illness; (5) People with severe autoimmune diseases.

1.3 Detection method

(1) ANGPTL4 detection method: Immediately after admission of the two groups of subjects, cubital venous blood was drawn and placed at room temperature for 1 hour, centrifuged, and stored at -80°C for testing. Double antibody sandwich enzyme-linked immunosorbent assay (ELISA) was used to detect the level of ANGPTL4. The kit was purchased from R&D in the United States, and the kit was operated in strict accordance with the kit instructions.

(2) Atherosclerosis: After the two groups of study subjects were admitted to the hospital, digital color Doppler ultrasound was used to measure their carotid artery intima-media thickness (CIMI) and the largest area of plaque, and to determine the carotid artery Atherosclerosis Crouse score (the maximum thickness of each isolated plaque in the carotid arteries on both sides).

(3) Biochemical indicators: Fasting venous blood was drawn in the morning after 8 hours of fasting for the two groups of subjects, and their fasting blood glucose (FPG) was measured; their insulin (FINS) level was measured by an automatic electrochemiluminescence analyzer; hydroxylamine was used The method was used to detect the superoxide dismutase (SOD); the tumor necrosis factor-α (TNF-αwas detected by ELISA; the blood lipids and homocysteine were detected by an automatic biochemical analyzer.

1.4 Observation indicators

(1) ANGPTL4 level: Measure the expression of ANGPTL4 in the two groups of subjects.

(2) Atherosclerosis: Check the CIMI and the largest plaque area of the observation group and count their Crouse points.

1.5 Statistical processing

SPSS 22.0 statistical software was used to analyze the data. Among them, the measurement data conforming to the normal distribution are

represented by the mean ± standard deviation (±s), the comparison between groups is by t test; the count data is represented by the number of cases (n) or percentage (%), and the data comparison is by the χ2 test. When P <0.05, the difference is statistically significant.

2. Results

2.1 Comparison of two groups of general information

Comparing the gender, average age, and body mass index (BMI) of the two groups, it was found that there was no significant difference between the two groups, which was not statistically significant (P>0.05). See Table 1.

Table 1. **Comparison of general information between the two groups**

Group		Observation group（n=60）	Control group （n=60）	Statistics	P value
Gender (example)	Male	35	34	10.327	0.264
	Female	25	26		
Average age (years)		60.48±8.29	60.25±8.21	10.520	0.068
BMI（kg/m^2）		22.48±5.29	22.85±2.03	10.648	0.094

2.2 Comparison of ANGPTL4 expression and clinical biochemical index levels in the two groups

The serum ANGPTL4 expression levels and clinical biochemical indicators were compared between the two groups. The results showed that the ANGPTL4 expression levels, TG, and SOD of the observation group were significantly lower than those of the control group, and the differences were statistically significant (P<0.05); TC, HDL-C, LDL-C, FPG, FINS, TNF-α CIMT, maximum plaque area and Crouse score were significantly higher than those of the control group, and the differences were statistically significant (P<0.05), see Table 2.

Table 2**. Comparison of ANGPTL4 expression in the two groups in terms of clinical biochemical index levels**

Group	Observation group（n=60）	Control group （n=60）	T value	P value
ANGPTL4（ng/ml）	30.46±4.26	36.15±3.59	6.214	0.005
TC（mmol/L）	5.86±0.26	4.56±0.28	5.268	0.001
TG（mmol/L）	1.86±0.16	1.60±0.18	6.327	0.002
HDL-C（mmol/L）	1.12±0.35	1.55±0.48	6.597	0.018
LDL-C（mmol/L）	3.26±0.44	2.71±0.30	6.297	0.006
FPG（mmol/L）	8.86±3.01	5.03±0.86	5.268	0.005
FINS（mU/L）	9.33±2.48	7.59±1.48	5.973	0.002
SOD（U/mL）	82.45±7.12	97.56±9.45	6.201	0.027
TNF-α（ng/L）	41.56±8.59	35.21±6.20	5.624	0.015
CIMT（mm）	0.96±0.10	0.66±0.05	5.268	0.002
Maximum area of plaque（mm^2）	0.34±0.04	0.16±0.01	5.624	0.001
Crouse Points (points)	8.15±0.99	5.66±0.61	6.264	0.002

2.3 Correlation between ANGPTL4 level and other indicators

According to Pearson analysis, the expression level of ANGPTL4 was positively correlated with TG and SOD levels (P<0.05), and negatively correlated with LDL-C, FPG, FINS, CIMT, the largest area of plaques, and Crouse levels (P<0.05). See Table 3 and Figure 1.

2.4 Multi-element regression analysis of factors affecting serum CIMT levels

The results of multi-element regression analysis of patients' serum CIMT levels showed that ANGPTL4 and TNF-αare independent influencing factors of patients' CIMT.

2.5 Multivariate regression analysis of carotid atherosclerosis in patients with ACI

Regression analysis of multiple factors affecting carotid atherosclerosis in patients with ACI found

that age, smoking history, hypertension, and ANGPTL4 level were the factors affecting carotid atherosclerosis (P<0.05). See Table 5.

Table 3. **Correlation between ANGPTL4 level and other indicators**

Project	R value	P value
age	0.351	0.215
TC	0.326	0.264
TG	0.526	0.015
HDL-C	0.321	0.277
LDL-C	-0.499	0.022
FPG	-0.578	0.006
FINS	-0.628	0.002
SOD	0.625	0.003
TNF-α	-0.551	0.024
CIMT	-0.754	0.001
Maximum area of plaque	-0.659	0.005
Crouse integral	-0.664	0.003

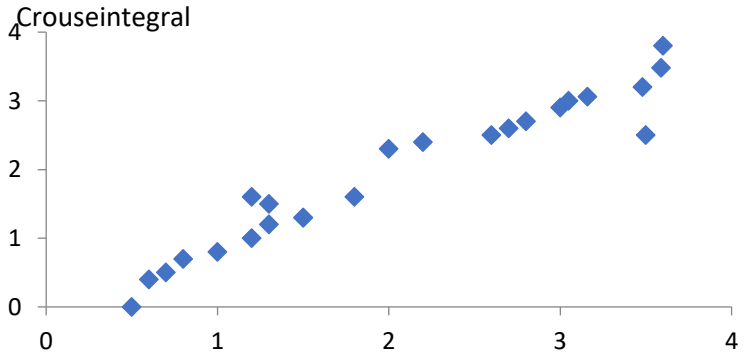

Figure 1. **ANGPTL4 level and Crouse product dispersion point trend graph**

Table 4. **Multivariate regression analysis of factors affecting serum CIMT levels**

Project	Regression coefficients	Standard error	Standardized regression coefficient	T value	P value
Constant	0.124	0.105	-	1.330	0.162
ANGPTL4	-0.201	0.095	-0.362	-2.652	0.007
TNF-α	0.256	0.095	0.326	2.501	0.018

Table 5. **Multivariate regression analysis of carotid atherosclerosis in patients with ACI**

Factor	β value	S.E value	Wald value	P value	OR value	95%CI
Gender	0.036	0.046	0.532	0.075	0.965	0.421~2.154
Age	0.596	0.267	5.264	0.018	1.264	1.659~2.018
Cardiac function level	0.015	0.648	0.042	0.058	0.451	0.954~1.264
Smoking	0.541	0.524	16.248	0.005	1.242	0.698~1.957
Drinking	0.502	0.164	0.954	0.064	0.264	0.621~1.089
Hypertension	0.406	0.128	7.021	0.012	1.027	1.485~2.038
Diabetes	0.523	0.267	9.264	0.002	0.264	0.264~1.008
Hyperlipidemia	0.216	0.521	0.145	0.264	0.267	0.948~1.264
TC	0.086	0.268	1.264	0.564	0.648	0.954~1.465
TG	0.265	0.621	0.154	0.264	0.649	0.459~1.028
LDL-C	0.056	0.594	0.264	0.089	0.542	0.154~1.294
HDL-C	0.264	0.564	0.268	0.068	0.268	0.024~1.158
ANGPTL4	0.254	0.348	4.289	0.002	2.154	1.326~3.018

3. Discuss

Atherosclerosis is a chronic vascular disease. It plays an important role in the occurrence and progression of atherosclerosis, especially in the rupture of atherosclerotic plaque and the activation of platelets in thrombosis [8]. The occurrence of atherosclerosis mainly includes the damage of endothelial cells, the accumulation of a large amount of lipids in the intima, the enhancement of various immune responses, the increase of smooth muscle cells in the vascular intima, and the formation of atherosclerotic plaques [9]. Atherosclerosis is the pathological basis of cerebrovascular disease, an important cause and risk factor of ischemic cerebrovascular disease. For patients with atherosclerosis, the probability of acute cerebral infarction is much higher than that of no artery people with atherosclerosis. In clinical studies, it has been found that for patients with atherosclerosis in ACI, the expression level of ANGPTL4 in their serum is significantly different from than that of normal people [10].

As a secreted glycoprotein, ANGPTL has a wide range of biological effects. Studies have shown that the vast majority of ANGPTL can participate in the regulation of angiogenesis, while a small number of ANGPTL can affect lipids and glucose [11]. Among them is a newly discovered vascular protein factor, which can be expressed in humans and mice. In mice, ANGPTL4 is highly expressed in adipose tissue, and low in heart, liver, ovary and other tissues; while in humans, ANGPTL4 protein is mainly expressed in the liver in cells, and in adipose tissue, plasma, Low expression in the placenta and heart [12]. According to related studies [13], the expression of ANGPTL4 protein is affected by many factors, among which its surrounding environment is the main influencing factor. ANGPTL4, as a new type of inflammatory adipokines, can convert active lipoprotein lipase fragments into inactive monomers, thereby inhibiting the activity of protein lipase, resulting in reduced lipid absorption capacity and atherosclerotic the progress is reduced, thereby exerting an anti-hardening effect [14]. In addition, according to related studies, ANGPTL4 is also closely related to lipid metabolism and glucose metabolism. When the level of ANGPTL4 is high, fat deposition is reduced [15]. In addition to affecting the metabolism of lipoprotein lipase, ANGPTL4 has an effect on atherosclerosis. It can also affect atherosclerosis in other ways. ANGPTL4 can hinder the vascular endothelial growth factor signal system, thereby weakening the signal transduction of tyrosine kinase, reducing the activity of myosin light chain kinase and the permeability of endothelial cells mediated by myosin light chain kinase [16]. In addition, inhibiting the tyrosine kinase signal transduction system can also prevent the phosphorylation of vascular endothelial growth factor receptor 2 and the formation of tyrosine kinase receptor complexes, up-regulate the expression of cadherin, and increase the stability of cell adhesion in order to maintain the integrity of endothelial cells [17].

In the research of Fernández-Hernando, et al. [18] scholars found that ANGPTL4 can exert an effect on carotid atherosclerosis in diabetic patients by affecting lipid metabolism. In the study of Yang L et al. [19], it was found that the up-regulation of ANGPTL4 expression has the effect of promoting angiogenesis, and ANGPTL4 can significantly inhibit the expression of inflammatory genes, thereby affecting the heart function of patients. A study by Osumi H et al. [20] showed that for ACI patients, the content of ANGPTL2 is positively correlated with the maximum area of atherosclerotic plaque and CIMT. ANGPTL2 can be used as an indicator of atherosclerosis, which can be intuitive and reflects the severity of the condition of ACI patients. The role of ANGPTL4 in the human body, in recent years, a large number of studies have shown that it has multiple effects and is of great significance to the human body. Scholars such as Ying Xuejiao [21] found that the level of ANGPTL4 is closely related to glucose metabolism. ANGPTL4 can have an effect on hypothalamic adenylate protein kinase, and has an effect on food consumption, so it has an effect on sugar intake. Liu Jing et al [22] scholars found that ANGPTL4 can have an effect on lipid metabolism by blocking lipoprotein lipase. In the above-mentioned study, regarding the expression of ANGPTL4 in ACI patients, it was found that the expression level of ANGPTL4 in the serum of the observation group was significantly lower than that of the control group. This indicates that ANGPTL4 is up-regulated in ACI. This may be because ANGPTL4 affects ACI patients through its effect on carotid atherosclerosis. This is similar to the results of Zhou Shuaiyang et al. [23] studying the expression of ANGPTL4 in tumor cells. In the above studies, it was also found that the TG and SOD levels of the observation group were significantly lower than those of the control group, while TC, HDL-C, LDL-C, FPG, FINS, TNF-αCIMT, the largest area of plaque, and the Crouse score were all significantly higher than the control group. It further shows that TG, SOD and ANGPTL4 expression levels are positively correlated, while ANGPTL4 expression levels are negatively correlated with TC, HDL-C, LDL-C, FPG, FINS, TNF-α CIMT, the largest area of plaque, and

Crouse score. Furthermore, a multi-element regression analysis of IMT levels showed that ANGPTL4 and TNF-α are independent factors influencing patients' IMT. Multi-element regression analysis of carotid atherosclerosis in patients with ACI found that age, smoking history, hypertension and ANGPTL4 are all factors affecting carotid atherosclerosis. The above research data indicate that TNF-α plays an important role in carotid atherosclerosis, and the expression level of ANGPTL4 is negatively correlated with the level of TNF-α It is speculated that low levels of ANGPTL4 weaken the inhibitory effect of TNF-α and participate in transarterial occurrence of atherosclerosis. Oxidative stress also plays a role in carotid atherosclerosis, and studies have shown that high expression of ANGPTL4 can reduce oxidative stress and peroxidation. Therefore, ANGPTL4 can also have an effect on carotid atherosclerosis through oxidative stress. Studies have confirmed that lipid metabolism plays an important role in carotid atherosclerosis. And the expression of ANGPTL4 has a certain relationship with lipid metabolism. Therefore, it is speculated that ANGPTL4 can promote trans atherosclerosis by participating in the process of lipid metabolism. Previous studies on the factors affecting coronary artery stenosis in patients with coronary heart disease found that hypertension, age, and smoking all have an impact on coronary artery stenosis. Smoking can cause coronary artery endothelial damage, thereby promoting the degree of coronary artery stenosis. This is similar to the results of the above research.

To sum up, in ACI patients, the expression of ANGPTL4 is lower than that of healthy people. ANGPTL4 mainly affects the condition of ACI patients through its effect on carotid atherosclerosis. ANGPTL4 can participate in the regulation of lipid metabolism, reduce glucose metabolism, oxidative stress, inflammation, and the formation of new blood vessels to stabilize carotid atherosclerotic plaque and inhibit its further progress.

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