

Clinical significance of serum MCP-1 and VE-cadherin levels in patients with acute cerebral infarction

X. HE, D.-R. LI, C. CUI, L.-J. WEN

Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China

Abstract. – **OBJECTIVE:** Vascular injuries have been proposed to play a role in cerebral infarction (CI)-induced brain damage. In this study, the expressions of monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial-cadherin (VE-Cadherin) in patients with acute stroke was examined, and the clinical significance was analyzed.

PATIENTS AND METHODS: 102 patients with acute CI between February 2012 and 2015 were recruited in this study. Among these patients, 43 patients presented with progressive cerebral infarction (PCI) while 59 patients presented with non-progressive cerebral infarction (NPCI). The carotid intima-media thickness (IMT) of all patients was measured by ultrasound as a marker of end-organ damage. Our results showed that 26 patients had normal IMT, 19 patients had a thickening carotid wall and 57 patients presented with a carotid plaque. In our study, 52 healthy volunteers screened by medical check-ups in our hospital during the same period were taken as control group. The MCP-1 and VE-cadherin expressions in each group were detected and analyzed.

RESULTS: Compared to the control group, the patients in the experimental group had significantly elevated serum MCP-1 and VE-cadherin levels ($p < 0.05$). Compared to the NPCI patients, the serum MCP-1 and VE-cadherin levels of the patients with PCI were significantly increased, and the rate of carotid plaque was increased as well, especially in the mixed echo and low echo plaques. Then compared with the patients with normal IMT and thickening carotid wall, the patients with carotid plaques had notably increased MCP-1 and VE-cadherin levels.

CONCLUSIONS: For patients with PCI, the serum MCP-1 and VE-cadherin levels were significantly increased. Moreover, serum MCP-1 and VE-cadherin levels were correlated with atherosclerosis and the stability of atherosclerotic plaques in patients with cerebral infarction.

Key Words:

Endothelial cells, MCP-1, VE-cadherin, Cerebral infarction, Carotid artery disease.

Introduction

For the patients with acute cerebral infarction (ACI), 1 week after the ischemic stroke, the symptoms of neurological deficits in patients will aggravate stepwise. In some cases, patients develop into more severe neurological deficits, namely, progressive cerebral infarction (PCI)¹⁻³. The etiologic mechanism of progressive cerebral infarction is that the patients start to have atherosclerosis (AS). Local brain tissue in patients with ischemic reperfusion normally has uncontrolled and excessive inflammatory responses, which play a very important role in the occurrence and development of the disease. During the development of AS, monocyte chemotaxis protein 1 (MCP-1) plays a crucial role⁴. Also, among the major proteins for endothelial cell adhesion, VE-cadherin is one of the most important mediators involved in AS⁵. This study is mainly to analyze the main clinical significance of serum MCP-1 and VE-cadherin levels in patients with acute cerebral infarction, so as to provide a scientific reference value for the treatment of patients.

Patients and Methods

Patients

102 cases of patients with acute cerebral infarction between February 2012 and the end of 2015 were recruited as the research group. The average age for patients were 69.6±8.16 (ranging

from 60 to 80). There were 52 cases of male patients, and 50 female cases. Among the patients, 43 patients presented with PCI, in which 24 cases were male and 19 cases were females, with average 66.8 ± 7.37 years of age. 59 patients had non-PCI, including 31 male patients and 28 female patients with average 68.9 ± 7.83 years of age.

Inclusion Criteria

With a comprehensive diagnosis, the conditions of patients were all in accordance with the relevant diagnostic criteria drawn by the Fourth National Conference on Cerebrovascular Disease⁶. The conditions were as the following: the onset time was less than 72 h, the duration of symptoms was more than 24 h, and CT or MRI results showed that the cerebral infarction occurred in the corresponding cerebral function area by imaging examination. 52 cases of healthy volunteers in our Hospital during the same period were recruited as the control group, including 28 males and 24 females with an average age of 64.8 ± 9.43 years old (ranging from 60 to 85). The baseline characteristics of patients in research group and control group were compared, and the written consent forms were signed by all recruited patients.

Exclusion Criteria

The patients have the following situation through clinical examination were excluded: (1) History of cerebrovascular diseases, history of peripheral vascular diseases, and peripheral vascular diseases; (2) Patients with impaired neurological symptoms; (3) Patients with a malignant tumor, diabetes mellitus and other acute and chronic diseases; (4) Patients with myocardial infarction, angina, or the presence of severe pulmonary infection, upper respiratory tract infection, arthritis, cholecystitis and other infectious diseases; (5) Patients with tissue injury, immune disorders, liver and kidney dysfunction, or the recent use of anti-inflammatory drugs, etc.

Methods

Following treatment, the neurological function of patients was examined and scored daily⁸ to evaluate the degree of neurological impairment. Compared with the neurological function score at 6 h after the onset, if the patient's neurological function score increased by 1 point or more than 1 point from 6 h to 1 week after the onset, it could be considered as PCI⁴. If the patient has progressive cerebral infarction, it was necessary

to operate carotid artery ultrasound examination and measurement of carotid artery intima media thickness (IMT). The criteria of determination⁹ were: normal condition means carotid artery IMT is greater than or equal to 1.0 mm, but lower than 1.5 mm, when $IMT \geq 1.5$ mm, plaque is found in patients. There were 26 cases of normal IMT patients, 19 cases of IMT thickening, 57 cases of patients with a plaque.

The echogenicity of plaque has the following characteristics: (1) Dense echo is about the higher echo intensity on vascular walls, and more obvious sound images; (2) Mixed echo means the echo of plaque is not even; (3) Low echo shows more prominent plaque in the lumen, with comparison in the vascular wall, the echo intensity is relatively low, even with the same echo intensity in blood¹⁰. Volunteers in the control group were examined, and the blood sample was collected on the morning of the day after admission. Enzyme-linked immunosorbent assay (ELISA) double antibody sandwich method was used to measure the serum MCP-1 and VE-cadherin¹¹.

Statistical Analysis

The experimental data were analyzed by SPSS18.0 software (SPSS Inc., Chicago, IL, USA). All data are expressed as means plus or minus (\pm) standard deviation. Group data was using independent sample *t*-test and single factor analysis of variance. Count data used χ^2 -test, the difference $p < 0.05$ was statistically significant.

Results

Comparison of MCP-1 and VE-cadherin in Serum of Different Patients with IMT in the Experimental Group

Compared with the normal IMT patients, serum MCP-1 and VE-cadherin levels were significantly increased in patients with IMT thickening and plaques ($p < 0.05$). Compared with the IMT thickening patients, the serum levels of MCP-1 and VE-cadherin were significantly increased ($p < 0.05$) in the patients with plaque, as shown in Table I.

Comparison of Serum MCP-1 and VE-cadherin Levels in Each Group

Compared with the control group, the serum levels of MCP-1 and VE-cadherin were significantly increased in the experimental group ($p < 0.05$). Compared with the nonprogressive group,

Table I. Comparison of MCP-1 and VE-cadherin in serum of different patients with IMT.

Type	No.	MCP-1 (ng/L)	VE-cadherin (mg/L)
IMT Normal	26	268.3 ± 15.73	5.17 ± 1.02
IMT Thickening	19	287.4 ± 14.64	5.58 ± 1.14
Plaque	57	317.3 ± 18.31*#	6.47 ± 1.03*#

Note: *: Comparison with normal IMT, $p < 0.05$; #: Comparison to plaque, $p < 0.05$.

the levels of serum MCP-1 and VE-cadherin in patients with progressive cerebral infarction were significantly elevated, the difference was statistically significant ($p < 0.05$), as shown in Table II.

Comparison of Ultrasonic Features of Progressive Cerebral Infarction and non-PCI

Compared with the patients with non-progressive cerebral infarction, the detection rate of IMT thickening in patients with progressive cerebral infarction was decreased, the detection rate of mixed echo and low echo plaque was increased, the difference was statistically significant ($p < 0.05$), as shown in Table III.

Discussion

In the pathogenesis of stroke, AS is one of the most important causes¹². In cerebral infarction,

AS is one of the important risk factors for the occurrence and development of the disease^{13,14}. Moreover, the stability of plaque in AS disease is related to PCI^{15,16}. Previous reports^{17,18} have shown that MCP-1 plays an important role in the process of formation and rupture of plaque. There was a close relationship between the strength of leukocyte infiltration and the activity of MCP-1.

The results of this study showed that the serum levels of MCP-1 were significantly higher in the experimental group compared with the control group. Also, the MCP-1 level was positively associated with an increase in AS severity in the neck. Accumulating evidence has shown that^{19,20} the occurrence and development of AS has a direct effect on MCP-1, and the severity of AS positively correlates with the level of MCP-1. The results of this work are consistent with these previous researches.

The results of this study showed that the serum MCP-1 levels were significantly increased

Table II. Comparison of serum MCP-1 and VE-cadherin levels in each group

Type	No.	MCP-1 (ng/L)	VE-cadherin (mg/L)
Experimental group	102	304.2 ± 23.15#	6.11 ± 1.21#
Progressive cerebral infarction	43	313.3 ± 31.87*#	6.62 ± 1.37*#
Non-progressive cerebral infarction	59	298.4 ± 28.42#	5.89 ± 1.26#
Control group	52	219.6 ± 23.38	3.93 ± 1.21

Note: *: Comparison with non-progressive cerebral infarction, $p < 0.05$; #: Comparison with control group, $p < 0.05$.

Table III. Comparison of ultrasonic features of progressive cerebral infarction and non-progressive cerebral infarction.

Type	Progressive cerebral infarction (43 cases)	Non-progressive cerebral infarction (59 cases)	χ^2	p
IMT normal	4 (9.30)	12 (20.34)	2.291	0.130
IMT Thickening	1 (2.33)	14 (23.73)	9.084	0.003
Plaque				
Dense echo	5 (11.63)	18 (30.51)	5.077	0.024
Mixed echo	19 (44.19)	9 (15.25)	10.454	0.001
Low echo	16 (37.21)	9 (15.25)	6.480	0.011

in patients with progressive cerebral infarction compared with patients with non-progressive cerebral infarction. Regarding the plaque detection rate, the serum MCP-1 levels of the patients with progressive cerebral infarction were significantly higher than that of the non-progressive cerebral infarction. Moreover, as to the echo intensity of plaque, in particular the high plaque detection rate of mixed echo and low echo, our results showed that the level of serum MCP-1 was not only closely related to the clinical types of cerebral infarction and the severity of AS disease, but also had a certain correlation with the stability of AS plaque, which was in line with the previous findings²¹.

When the level of MCP-1 was increased, the instability of plaque was increased as well, and there was a certain correlation between the pathogenesis of cerebral infarction and the occurrence of unstable plaque^{22,23}. In recent years, there have been relevant clinical research results which clearly showed that increase in MCP-1 levels play an important role in the vulnerable part of AS plaque, and MCP-1 and chronic inflammation is closely related.

Conclusions

After the occurrence of AS, the VE-cadherin went into the blood. However, the mechanism of action remains unknown. We showed that the serum VE-cadherin levels of all types of cerebral infarction were significantly higher than those of the control group, suggesting that the development of cerebral infarction was accompanied by vascular endothelial cell injury²⁴. The level of VE-cadherin in the serum of patients with IMT thickening was not significant; however, the level of VE-cadherin in the serum of patients with a plaque was significantly elevated, which indicated that the levels of VE-cadherin in serum correlates with AS plaques. Therefore, we deduce the conclusions according to our findings²⁵. In the course of the formation of AS plaque *in vivo*, the injury of vascular endothelium elevated the level of VE-cadherin in serum. Immunohistochemical and histological study of carotid artery pathological sections²⁶ showed that the level of VE-cadherin was significantly increased in AS slices, especially in the area of the shoulder region in which plaque rupture occurred easily, and the edge of the fat core. It

suggested that the VE-cadherin is involved in the formation of AS plaque, and also related to the stability of the plaque. However, future histological studies are still needed for the further confirmation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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