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Correlations of acute myocardial infarction complicated by cerebral infarction with insulin resistance, adiponectin and HMGB1

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Abstract. – OBJECTIVE: To investigate the correlations of acute myocardial infarction (AMI) complicated by cerebral infarction with insulin resistance, adiponectin and high-mobility group box 1 (HMGB1).

PATIENTS AND METHODS: A total of 326 AMI patients receiving percutaneous coronary intervention (PCI) were selected as the research objects. They were divided into cerebral infarction group (n=24) and non-cerebral infarction group (n=302) based on their complication of cerebral infarction. In addition, 165 healthy people were enrolled as control group. Changes in the levels of HMGB1, adiponectin, fasting insulin (FINS), insulin sensitive index (ISI), insulin resistance, N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), interleukin-6 (IL-6), myocardial infarction markers and coagulation function indexes were compared among the three groups. Correlations among those indexes were analyzed.

RESULTS: AMI patients had higher levels of HMGB1, FINS, homeostasis model assessment of insulin resistance (HOMA-IR), ISI, creatine kinase isoenzyme (CK-MB), cardiac troponin I (cTnI), prothrombin time (PT), CRP and IL-6 than those in healthy participates, especially in those complicated with cerebral infarction. Conversely, levels of adiponectin, myoglobin (Mb), activated partial thromboplastin time (APTT), antithrombin III (AT-III), activated coagulation time (ACT) and NT-proBNP were the lowest in cerebral infarction group, and highest in control group ($p<0.05$). AMI complicated with cerebral infarction was negatively correlated with the levels of AT-III and adiponectin, but positively associated with the levels of NT-proBNP, HOMA-IR and HMGB1 ($p<0.05$).

CONCLUSIONS: AMI complicated with cerebral infarction has negative correlations with the levels of AT-III and adiponectin, but positively associated with the levels of NT-proBNP, HOMA-IR and HMGB1, possessing certain clinical significance in AMI treatment.

Key Words:
Acute myocardial infarction, Cerebral infarction, Insulin resistance, Adiponectin, HMGB1.

Introduction

With the elevated living standards, aggravated population aging, altered lifestyle and eating habits in China, the incidence rate of acute myocardial infarction (AMI) is rising year by year, and the number of hospitalized AMI patients increases relatively[1]. In recent years, large-scale implementation of multicenter evidence-based medicine trails and standardization of surgery have proposed. Interventional therapy and drug application for AMI patients significantly improve the therapeutic efficacy[2]. As revascularization for myocardial blood flow remodeling characterized by small traumas, simple and safe operations, percutaneous coronary intervention (PCI) can restore various cardiac functions and supply cerebral blood flow in preferable ways. However, AMI patients complicated with cerebral infarction have a fairly low incidence rate after PCI, posing great threats on the patient's life[3]. Studies[4] have manifested that inflammatory responses play vital roles in the treatment and restoration of AMI. High-mobility group box 1 (HMGB1), a pro-inflammatory cytokine or inflammatory mediator, which is related to AMI complicated with cerebral infarction to some extent. Adiponectin is a kind of polypeptide in the adipocyte, whose concentration is relatively low in coronary heart disease, diabetes mellitus and obesity. It is reported that adiponectin exerts certain effects on the pathogenesis of cerebral infarction in post-operative AMI patients[5]. Therefore, this paper aims

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to explore the relationships between AMI complicated with cerebral infarction and insulin resistance, adiponectin and HMGB1, thus providing references for clinical diagnosis and treatment.

Patients and Methods

Patients

This study was approved by the Ethics Committee of Haikou Hospital Affiliated to Xiangya School of Medicine, Central South University. Signed written informed consents were obtained from all participants before the study. A total of 326 AMI patients admitted and treated with PCI in our hospital from February 2016 to January 2018 were selected as the research objects. They were divided into cerebral infarction group (n=24) and non-cerebral infarction group (n=302) based on their complication of cerebral infarction. In addition, 165 healthy people receiving examinations in our hospital in the same time period were enrolled as control group. In cerebral infarction group, there were 14 males and 10 females aged 51-84 years old, with an average age of (63.21±5.67) years old and body mass index (BMI) of (22.67±1.20) kg/m^2. In terms of the infarction position, there were 19 cases of anterior infarction and 5 cases of non-anterior infarction. 17/24 AMI patients complicated with cerebral infarction were smokers. With regard to the underlying diseases, there were 5 cases of hyperlipemia, 7 cases of diabetes mellitus and 12 cases of hypertension. 15 patients had single lesion and 9 patients had multiple lesions. Non-cerebral infarction group consisted of 196 males and 106 females aged 50-85 years old, with an average age of (63.25±5.71) years old and BMI of (22.62±1.24) kg/m^2. In terms of the infarction position, there were 198 cases of anterior infarction and 104 cases of non-anterior infarction. There were 161/302 AMI patients in non-cerebral infarction group were smokers. As for the underlying diseases, there were 65 cases of hyperlipemia, 89 cases of diabetes mellitus and 148 cases of hypertension. 156 patients had single lesion and 146 patients had multiple lesions. There were 96 men and 69 women aged 50-85 years old, with an average of (64.01±5.58) years old and BMI of (22.54±1.15) kg/m^2, in control group. The general data such as age, gender and BMI had no significant differences among the three groups of participants, which were comparable (p>0.05).

Diagnostic Criteria

Diagnostic Criteria for AMI

According to the provisions on the AMI diagnostic criteria proposed by the WHO[6], inclusive criteria for AMI were as follows: 1) medical history: patients had a history of severe typical chest pain for more than half an hour. 2) Electrocardiogram: patients had abnormal electrocardiograms such as persistent QS wave, Q wave, symmetrically inverted T wave, progressive current of injury, stationary current of injury and current conduction disturbance during routine electrocardiogram examinations. 3) Serum enzyme: patients had sequential changes in myocardial enzyme, troponin and other related serum enzymes, which were first elevated and then decreased. Patients met any two of the above-mentioned criteria could be diagnosed with AMI.

Diagnostic Criteria for Cerebral Infarction

In accordance with the diagnostic criteria for acute ischemic stroke[7], the detailed criteria were as follows: the disease occurred rapidly within two weeks; the signs and symptoms continued for several hours after onset; the carotid intima-media thickness was greater than 1 mm; and Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) examinations showed major indications of cerebral infarction on condition that other lesions were excluded.

Inclusion and Exclusion Criteria

Inclusion criteria: 1) patients met the above-mentioned diagnostic criteria for AMI and cerebral infarction and 2) patients and their families agreed with and actively cooperated in this research and signed the informed consent. Exclusion criteria: 1) patients complicated with serious cardiac, hepatic or renal dysfunction, 2) patients complicated with Alzheimer's disease, autoimmune disease, nephrotic syndrome or malignant tumor, 3) patients with severe infection recently, 4) patients in pregnancy or lactation, 5) patients with advanced heart disease but without operative indications, or with moderate to severe aortic insufficiency, 6) patients with ruptured sinus aneurysm, aortic aneurysm or aortic dissecting aneurysm, 7) patients with ventricular fibrillation or cardiac arrest, 8) patients with aortoiliac occlusive disease, aortic dissection or aortic sinus aneurysm, or 9) patients who had poor compliance or withdrew halfway.

Therapeutic Methods

After admission to hospital, all the AMI patients were given oxygen inhalation and bed rest, administered with 300 mg clopidogrel (NMPN H20123115, Lepu Pharmaceuticals Co., Ltd., Beijing, China) and 300 mg aspirin enteric-coated tablets (NMPN H20065051, Shenyang Original Pharmacolabo Co., Ltd., Shenyang, China) and treated with PCI. Moreover, the patients underwent implantation of temporary pacemaker according to their disease conditions, and those with cardiac insufficiency received treatment with counter pulsation with intra-aortic balloon pump (IABP). The specific procedures were as follows: the femoral artery of the patients was punctured under sterile conditions. The balloon catheter was inserted under the guidance of X-ray positioning, and the balloon was placed into the descending aorta below the left clavicle. Then the IABP (AUTO CAT2 type, Arrow, Monroe Township, NJ, USA) was connected to trigger the pressure at a proportion of 1:1 and performed counter pulsation at the same time. After that, the proportion was changed to 1:2, and the IAB was stopped until the hemodynamics of the patients became stable.

Observation Indexes

1) The fasting venous blood was drawn from the elbow of every participant at about 8 o'clock in the next morning after fasting overnight for at least 8 h, which was placed at room temperature for 30 min and then centrifuged using a centrifuge [Ortho BioVue, Johnson & Johnson (Shanghai, China) Medical Company, Shanghai, China] with a centrifugal radius of 10.5 cm at 3,000 r/min for 10 min. Next, the supernatant was taken and preserved in a refrigerator at -75°C for detection. Enzyme-linked immunosorbent assay was utilized to measure serum levels of adiponectin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), HMGB1 and interleukin-6 (IL-6) using commercial kits purchased from Shanghai Yaoyun Biological Technology Co., Ltd. (Shanghai, China). Immune turbidimetry was applied to determine serum level of C-reactive protein (CRP). 2) Measurement of three markers of myocardial infarction: The levels of creatine kinase isoenzyme (CK-MB), cardiac troponin I (cTnI) and myoglobin (Mb) were detected by Triage immunofluorescence detector using commercial kits provided by Randox Laboratories Ltd. (London, UK). 3) Measurement of blood coagulation indexes: the activated partial thromboplastin time (APTT), prothrombin time (PT), antithrombin III (AT-III) and activated coagulation time (ACT) of the patients were detected using a full-automatic coagulation analyzer (STA-R Evolution, Seine, France). 4) Measurement of fasting insulin (FINS), insulin sensitive index (ISI) and insulin resistance levels: Serum level of FINS was determined by means of sandwich chemiluminescence immunoassay using a full-automatic chemiluminescence immunoassay analyzer (BMbio 400Plus, Baiming Biotechnology Company Limited, Yancheng, China) and supporting insulin assay kits. The content of fasting plasma glucose (FPG) was measured through hexokinase method and glucose detection kit (Dirui Industrial Co., Ltd., Changchun, China). Homeostasis model assessment of insulin resistance (HOMA-IR) index was adopted for evaluation. HOMA-IR = FINS (mIU/L) × FPG (mmol/L)/22.5. ISI = -ln (FPG × FINS)[8].

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 19.0 (SPSS Inc., Armonk, NY, USA) software was utilized to process the data. The measurement data were presented as ($\bar{x}\pm s$), and *t*-test was performed. The enumeration data were expressed by ratio, and χ^2-test was conducted. Spearman's correlation coefficient for ranked data was adopted for correlation analysis. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of HMGB1 and Adiponectin Levels Among the Three Groups of Participants

HMBG1 level remained the lowest in control group, but the highest in cerebral infarction group. Conversely, adiponectin level remained the highest in control group, but the lowest in cerebral infarction group ($p<0.05$) (Table I).

Comparisons of FINS, ISI and Insulin Resistance Levels Among the Three Groups of Participants

Levels of FINS, HOMA-IR and ISI were higher in AMI patients compared with those of healthy controls, which were the most pronounced in AMI patients complicated with cerebral infarction ($p<0.05$) (Table II).

Table I. Comparisons of HMGB1 and adiponectin levels among the three groups of participants.

	HMGB1 (μg/mL)	Adiponectin (mg/L)
Control group (n=165)	5.24±1.38	11.98±5.62
Non-cerebral infarction group (n=302)	18.13±6.75	8.76±4.25
Cerebral infarction group (n=24)	24.52±8.61	5.62±3.11
F	16.352	23.254
p	<0.001	<0.001

Table II. Comparisons of FINS, ISI and insulin resistance levels among the three groups of participants.

	FINS (mU/L)	HOMA-IR	ISI
Control group (n=165)	9.78±2.69	1.03±0.21	3.62±0.58
Non-cerebral infarction group (n=302)	15.36±3.85	1.36±0.31	4.29±0.66
Cerebral infarction group (n=24)	23.69±4.94	1.62±0.35	5.29±0.72
F	6.594	9.516	38.924
p	<0.001	<0.001	<0.001

Table III. Comparisons of levels of three markers of myocardial infarction among the three groups of participants.

	CK-MB (μg/L)	cTnI (μg/L)	Mb (g/L)
Control group (n=165)	19.86±4.23	4.16±1.08	200.32±31.26
Non-cerebral infarction group (n=302)	21.25±4.52	5.03±1.36	142.62±26.98
Cerebral infarction group (n=24)	24.63±5.23	8.14±1.69	89.75±23.45
F	52.364	6.721	18.706
p	<0.001	<0.001	<0.001

Table IV. Comparisons of blood coagulation index levels among the three groups of participants.

	APTT (s)	PT (s)	AT-III (mg/L)	ACT (s)
Control group (n=165)	41.25±6.52	11.01±0.59	221.65±61.25	157.33±48.67
Non-cerebral infarction group (n=302)	36.84±5.98	12.85±0.69	165.32±53.21	143.55±42.91
Cerebral infarction group (n=24)	33.52±5.69	14.25±0.96	142.38±45.39	137.26±38.35
F	30.265	21.069	15.624	17.328
p	<0.001	<0.001	<0.001	<0.001

Comparisons of Levels of Three Markers of Myocardial Infarction Among the Three Groups of Participants

Levels of CK-MB and cTnI were higher in AMI patients relative to healthy controls, especially in those complicated with cerebral infarction. Mb level showed the opposite trend in them ($p<0.05$) (Table III).

Comparisons of Blood Coagulation Index Levels Among the Three Groups of Participants

Serum levels of APTT, AT-III and ACT were the lowest in cerebral infarction group, but highest in control group. However, PT level was the highest in healthy controls, and lowest in AMI patients complicated with cerebral infarction ($p<0.05$) (Table IV).

Comparisons of NT-proBNP, CRP and IL-6 Levels Among the Three Groups of Participants

NT-proBNP level declined gradually, and the CRP and IL-6 levels were raised gradually in the participants in control group, non-cerebral infarction group and cerebral infarction group sequentially, displaying statistically significant differences ($p<0.05$) (Table V).

Correlations of AMI Complicated with Cerebral Infarction With Relevant Indexes

AMI complicated with cerebral infarction was negatively correlated with the levels of AT-III and adiponectin and positively associated with the levels of NT-proBNP, HOMA-IR and HMGB1 ($p<0.05$) (Table VI).

Table V. Comparisons of NT-proBNP, CRP and IL-6 levels among the three groups of participants.

	NT-proBNP (ng/L)	CRP (mg/L)	IL-6 (mg/L)
Control group (n=165)	315.84±36.29	2.78±1.25	2.08±0.94
Non-cerebral infarction group (n=302)	677.32±59.82	38.45±8.63	4.66±1.27
Cerebral infarction group (n=24)	987.1±98.63	44.67±9.52	8.25±1.64
F	7.521	8.235	11.975
p	<0.001	<0.001	<0.001

Discussion

A majority of AMI patients usually have plaque rupture, vasospasm and bleeding, which trigger thrombosis and acute tubal occlusion. Serious ischemic symptoms in the myocardium supplied by the vessels eventually lead to necrosis. Therefore, AMI patients are often complicated with arrhythmia, cardiac insufficiency, cardiogenic shock, ventricular aneurysm and cerebral infarction[9]. Some studies have argued that cerebral infarction may be formed because of degenerated and coarse endocardium after AMI, resulting in platelet adhesion, mural thrombosis and detachment. Ventricular remodeling occurs at post-AMI, and some patients will have a certain degree of atrial fibrillation, thereby leading to dysregulated hemodynamics and mural thrombosis in the atrium. Moreover, the detached endocardium can block the branches of internal carotid artery system[10]. Generally, multiple organs are affected in AMI patients due to atherosclerosis, of which the most seriously affected is the cardiocerebrovascular system, further triggering myocardial and cerebral infarction[11]. Ventricular aneurysm formation after AMI is also an important reason for mural thrombosis in the heart, whose detachment can form embolism. Many pathological lesions occur after AMI, including massive myocardial infarction, decreased myocardial contractibility, blood flow velocity, blood pressure and cardiac output, insufficient cerebral perfusion, and thrombus formation on the basis of cerebral atherosclerosis[12]. AMI can also stimulate the motor center in the brain stem, promote disturbance of cerebral blood flow and induce cerebral infarction. In this paper, changes in the coagulation functions and correlation results may be caused by the fact that ACT and AT-III were indexes capable of comprehensively reflecting the coagulation state in the body, indicating the therapeutic effects of heparin drugs favorably. It is argued in studies that the anticoagulation effect of heparin responded poor in the body when the AT-III activity was lower than 70%, and a certain degree of heparin resistance occurred. In the case of reduced AT-III activity, the body's sensitivity to corning is strengthened, and the ultimate therapeutic effect is unfavorable, thus aggravating thrombosis to some extent and leading to cerebral infarction[13]. Adiponectin mainly deposits in human arterial walls and can repress the expressions of E-selectin, intercellular adhesion molecule and vascular cell adhesion molecule in the endothelial cells, further decreasing the adhesion of monocytes to human aortic endothelial cells[14]. It can inhibit the phagocytic activity of mature macrophages and the production of TNF-α, thereby significantly inducing the apoptosis of bone marrow monocytes. In addition, adiponectin is able to negatively regulate the body immune response and blood cell generation, which suppresses the occurrence of inflammatory responses[15]. In the granulation or early-stage AMI, adiponectin is primarily distributed in myocardial cells surviving around the focus and interstitial tissues, exerting a crucial role in the mechanism of ventricular remodeling after AMI and induces embolism of the carotid artery system[16]. The elevated level of HOMA-IR, is an index capable of comprehensively indicating atherosclerosis, lipid metabolism disorder, hypertension and diabetes mellitus in the body. High expression of HOMA-IR indicates a high risk of AMI complicated with cerebral infarction after operation. There is a positive correlation between HOMA-IR and the diseases[17]. The inflammatory responses in the body are leading causes of cor-

Table VI. Correlations of AMI complicated with cerebral infarction with relevant indexes.

	r	*p*
NT-proBNP	3.575	<0.001
AT-III	-0.543	<0.001
HOMA-IR	0.781	0.005
HMGB1	0.537	0.014
Adiponectin	-0.368	<0.001

onary atherosclerosis instability in AMI patients. Inflammation can activate the endothelial cells in some degree, increase the expressions of inflammatory genes and leukocyte cell adhesion molecules, aggravate platelet aggregation and plaque instability and cause plaque rupture, thus stimulating myocardial ischemia and thrombosis[18]. As a vital inflammatory mediator, HMGBI can certainly promote the secretion of inflammatory factors and activation of inflammatory cells. The elevated HMGBI level can enhance the adhesion of monocytes, increase the secretion of cytokines and pro-inflammatory mediators, exacerbate thrombosis and plaque rupture and form mural thrombus, finally triggering cerebral infarction[19]. Studies have demonstrated that NT-proBNP is an important risk factor for AMI patients complicated with cerebral infarction. The possible reason is that a particular hypercoagulable state is formed under the actions of vasoactive substances and platelets after AMI. Increased risk of secondary mural thrombosis and thrombus detachment subsequently lead to cerebral infarction[20].

Conclusions

AMI complicated with cerebral infarction has negative correlations with the levels of AT-III and adiponectin, which is positively associated with the levels of NT-proBNP, HOMA-IR and HMGB1, possessing certain clinical significance.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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