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Journal of Acute Disease

journal homepage: www.jadweb.org

Original article http://dx.doi.org/10.1016/j.joad.2016.04.002

Correlation between the condition of patients with acute cerebral infarction and serum β2-microglobulin levels

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ARTICLE INFO

Article history:
Received 28 Feb 2016
Received in revised form 17 Mar 2016
Accepted 15 Apr 2016
Available online 9 Jun 2016

Keywords:
Acute cerebral infarction
β2-microglobulin
Inflammatory factor
Chemotactic factor

ABSTRACT

Objective: To observe the correlation between the condition of patients with acute cerebral infarction and serum β2-microglobulin (β2-MG) levels.

Methods: Patients with acute cerebral infarction and healthy physical examinees selected for the prospective study were included into the cerebral infarction group and control group, respectively. Clinical data were collected and the patients' condition were evaluated, and then the contents of the β2-MG, high sensitivity C reactive protein (hsCRP), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), intercellular cell adhesion molecule-1 (ICAM-1) and soluble CD40 Ligand (sCD40L) in serum were tested.

Results: The contents of serum β2-MG, hsCRP, IL-6, IL-8, TNF-α, ICAM-1, sCD40L in patients with acute cerebral infarction were obviously higher than those in cases of the control group. The severer the condition of the disease was, the higher contents of serum β2-MG, hsCRP, IL-6, IL-8, TNF-α, ICAM-1 and sCD40L became. The greater the volume of cerebral infarction was, the higher the contents of serum β2-MG, hsCRP, IL-6, IL-8, TNF-α, ICAM-1 and sCD40L were. The content of serum β2-MG was positively associated with the contents of hsCRP, IL-6, IL-8, TNF-α, ICAM-1 and sCD40L.

Conclusions: The level of serum β2-MG was abnormally elevated in the patients with acute cerebral infarction. The level of serum β2-MG can evaluate the severity of disease, infarction size and the degree of inflammation reaction in patients with acute cerebral infarction.

1. Introduction

Acute cerebral infarction is a common cerebrovascular disease with high disability rates and fatality rates, which is an important and difficult point in clinical treatment[1,2]. The pathophysiological process after the occurrence of the ischemic infarction in brain tissue is very complicated and is not yet entirely clear. Inflammation reaction, cell apoptosis, and oxidative stress injury are proved to be closely related to cerebral infarction[3–5]. The inflammation reaction, which is abnormally activated by the infarctions focus, is the key part of causing the injury of neural function and the development of the cerebral infarction. Various inflammatory factors [C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6)] and adhesion molecules intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1, soluble CD40 ligand (sCD40L)] also participate in this process[6–8]. The contents of inflammatory factors and adhesion molecules can reflect the severity of cerebral infarction in some extent, however, due to the complex process of the inflammation reaction and the involvement of multiple links, and the changed cytokines in serum of different patients with cerebral infarction might have differences, which cause the condition of disease cannot be accurately evaluated through the detection of single cytokine.

In recent years, clinical scholars have devoted to search for a serum index that can accurately evaluate the patients' condition of cerebral infarction. β2-microglobulin (β2-MG) is the micromolecular protein separated from tubular proteinuria by

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Foundation project: Supported by the Key Project of Sichuan Health Department (Grant No. 060039).

Peer review under responsibility of Hainan Medical College. The journal implements double-blind peer review practiced by specially invited international editorial board members.

Berggård[9]. Its molecular weight is 12 kD, which widely distributes in almost all human cells except erythrocytes and placenta trophocytes, and it was mainly composed and secreted by lymphocytes, neutrophile granulocytes, mononuclear macrophages and mesenchymal cells. The synthetic rate and clearance rate of *in vivo* β2-MG maintain a relative balance. The content of β2-MG in serum will be abnormally elevated when β2-MG is over-compounded or the elimination becomes difficult. The numbers of lymphocytes, neutrophile granulocytes and mononuclear macrophages will be significantly increased when body's inflammatory reaction was activated, which causes the increase of the synthesis of β2-MG[10,11]. As previously mentioned, the activation of inflammatory reaction is an important link in the development of the acute cerebral infarction. Therefore, we speculated that in the process of the occurrence of acute cerebral infarction, the activation of the inflammatory reaction can increase the numbers of multiple inflammatory cells, and then increase the synthesis of β2-MG. The severity condition of patients with cerebral infarction can be evaluated by detecting the content of serum β2-MG. In order to verify this speculation, we analyzed the correlation between the condition of patients with acute cerebral infarction and serum β2-MG levels.

2. Materials and methods

2.1. Group cases

A prospective study was carried out after setting the inclusion criteria and exclusion criteria, including the cerebral infarction group and control group. The study has been approved by the Hospital Ethics Committee, and patients in groups signed the informed consent. Patient with acute cerebral infarction was selected as research objects in the cerebral infarction group. The inclusion criteria required patients to meet the academic standards by The Chinese Neuroscience Society and The Chinese Neurosurgical Society[12], and patients suffering from cerebral infarction for the first time and admitting to hospital within 24 h proved to have infarction by emergent CT after admission. Patients combined with severe heart and lung diseases or hepatic and renal dysfunction and patients with the history of an infection in recent 1 month were excluded. Research objects in the control group were all selected from the physical examination center of our hospital. Their gender, age and body mass index (BIM) matched with those of patients in the cerebral infarction group, and patients with cerebrovascular disease and liver and kidney dysfunction were excluded after physical examination.

2.2. Study methods

Gender, age, height, weight, cases of hypertension, diabetes, hyperlipidemia and smoking history of patients of the two groups were collected in accordance with the case data of patients in the cerebral infarction group and the medical examination reports of healthy objects in the control group. Patients with cerebral infarction received scores of National Institutes of Health Stroke Scale (NIHSS) after admission. The scores less than 7 were mild cases, 7–15 were moderate cases, more than 15 were serious cases. The volume of cerebral infarction was calculated according to Pullicino formula after conducting emergency CT.

Cerebral infarction volume = length (cm) × width (cm) × scanned positive layers/2.

The hematoma volume < 4 cm^3 was considered as small-size infarction; 4–10 cm^3 was medium-size infarction; and > 10 cm^3 was large-size infarction. On admission, 10 mL peripheral venous blood of patients with cerebral infarction was collected immediately, and also 10 mL peripheral venous blood of healthy people in the control group was collected at physical examination. Blood were placed at room temperature for 10–15 min, and centrifuged at 3 000 r/min for 10 min to collect the upper serum and the contents of β2-MG, high sensitivity C reactive protein (hsCRP), IL-6, IL-8, TNF-α, ICAM-1, sCD40L were tested by ELISA.

2.3. Statistical analysis

Data were analyzed by SPSS version 19.0. Measurement data were all expressed with mean ± SD. Data between two groups were analyzed by *t*-test, and data among three groups were analyzed by ANOVA. Enumeration data were expressed by frequencies and analyzed by *Chi*-square test. Correlations between two variables were tested by Pearson's correlation analysis. Differences were statistically significant ($P < 0.05$).

3. Results

3.1. General clinical data of objects in the two groups

Among 62 cases in the cerebral infarction group, 38 of them were males and 24 were females with ages ranging from (54.1 ± 9.8) years and the BMI of (22.92 ± 2.83) kg/m^2. There were 35 cases of hypertension, 18 cases of diabetes and 26 cases of smoking history. The concent of triglyceride was (1.71 ± 0.20) mmol/L, cholesteryl ester was (4.62 ± 0.51) mmol/L, urea nitrogen was (5.29 ± 0.55) mmol/L, and serum creatinine was (68.12 ± 7.96) μmol/L. Among 65 cases in the control group, 40 cases of them were males and 25 cases were females with ages ranging from (55.7 ± 8.4) years and the BMI of (22.53 ± 2.75) kg/m^2. There were 9 cases of hypertension, 4 cases of diabetes, 8 cases of smoking history, and the contents of triglyceride, cholesteryl ester, blood urea nitrogen and serum creatinine were (1.78 ± 0.18) mmol/L, (4.49 ± 0.64) mmol/L, (5.44 ± 0.62) mmol/L and (66.38 ± 7.57) μmol/L, respectively (Table 1).

Table 1
Clinical data of patients in the two groups.

Terms	Cerebral infarction group (n = 62)	Control group (n = 65)	P
Gender (male/female)	38/24	40/25	> 0.05
Age (year)	54.10 ± 9.80	55.70 ± 8.40	> 0.05
BMI (kg/m^2)	22.92 ± 2.83	22.53 ± 2.75	> 0.05
Hypertension	35 (56.45%)	9 (13.85%)	< 0.05
Diabetes	18 (29.03%)	4 (6.15%)	< 0.05
Smoke	26 (41.94%)	8 (12.31%)	> 0.05
Triglyceride (mmol/L)	1.71 ± 0.20	1.78 ± 0.18	> 0.05
Cholesteryl ester (mmol/L)	4.62 ± 0.51	4.49 ± 0.64	> 0.05
Blood urea nitrogen (mmol/L)	5.29 ± 0.55	5.44 ± 0.62	> 0.05
Serum creatinine (μmol/L)	68.12 ± 7.96	66.38 ± 7.57	> 0.05

3.2. Contents of serum β2-MG, inflammatory factors and adhesion molecules of patients in the two groups

The contents of β2-MG [(2.91 ± 0.34) *vs.* (1.28 ± 0.14) mg/L], hsCRP [(19.34 ± 2.41) *vs.* (2.96 ± 0.33) mg/L], IL-6 [(24.91 ± 2.63) *vs.* (9.84 ± 1.06) ng/L], IL-8 [(3.85 ± 0.41) *vs.* (0.78 ± 0.12) μg/L], TNF-α [(75.71 ± 12.48) *vs.* (20.44 ± 4.96) μg/L], ICAM-1 [(412.50 ± 56.40) *vs.* (147.60 ± 18.50) μg/L], sCD40L [(2.85 ± 0.35) *vs.* (1.14 ± 0.13) μg/L] in serum of the patients with acute cerebral infarction were obviously higher than those in control group (Table 2).

3.3. Contents of serum β2-MG, inflammatory factors and adhesion molecules in patients with different severity of cerebral infarction

The contents of serum β2-MG, hsCRP, IL-6, IL-8, TNF-α, ICAM-1 and sCD40L in patients with different severity of cerebral infarction were different. The severer condition of cerebral infarction led to the higher contents of serum β2-MG [(1.77 ± 0.20) *vs.* (2.51 ± 0.30 *vs.* (3.98 ± 0.44) mg/L], hsCRP [(10.14 ± 1.14) *vs.* (17.22 ± 2.33) *vs.* (29.22 ± 3.47) mg/L], IL-6 [(15.04 ± 1.78) *vs.* (23.41 ± 2.97) *vs.* (34.01 ± 3.33) ng/L], IL-8 [(1.78 ± 0.22) *vs.* (2.97 ± 0.35) *vs.* (5.91 ± 0.68) μg/L], TNF-α [(43.14 ± 5.89) *vs.* (72.33 ± 9.41) *vs.* (101.33 ± 16.22) μg/L], ICAM-1 [(302.10 ± 34.80) *vs.* (401.20 ± 50.20) *vs.* (572.30 ± 68.70) μg/L] and sCD40L [(1.77 ± 0.19) *vs.* (2.59 ± 0.29) *vs.* (4.47 ± 0.58) μg/L] (Table 3).

3.4. Contents of serum β2-MG, inflammatory factors and adhesion molecules in patients with different volume of cerebral infarction

There were differences among the contents of serum β2-MG, hsCRP, IL-6, IL-8, TNF-α, ICAM-1, sCD40L in patients with different volume of cerebral infarction. The greater volume of cerebral infarction resulted in the higher contents of serum β2-MG [(1.69 ± 0.19) *vs.* (2.65 ± 0.32) *vs.* (3.85 ± 0.41) mg/L], hsCRP [(9.48 ± 1.14) *vs.* (16.87 ± 2.19) *vs.* (30.49 ± 3.68) mg/L], IL-6 [(14.27 ± 1.95) *vs.*(22.13 ± 2.62) *vs.* (30.49 ± 3.68) ng/L], IL-8 [(1.66 ± 0.22) *vs.* (3.15 ± 0.39) *vs.* (5.57 ± 0.61) μg/L], TNF-α [(40.39 ± 5.38) *vs.* (69.48 ± 9.68) *vs.* (95.65 ± 14.59) μg/L], ICAM-1 [(289.50 ± 32.60) *vs.* (389.40 ± 47.90) *vs.* (597.70 ± 71.40) μg/L] and sCD40L [(1.89 ± 0.22) *vs.* (2.64 ± 0.31) *vs.* (4.18 ± 0.55) μg/L] (Table 4).

Table 2
Contents of serum β2-MG, inflammatory factors and adhesion molecules of patients in the two groups.

Terms	Cerebral infarction group (n = 62)	Control group (n = 65)	P
β2-MG (mg/L)	2.91 ± 0.34	1.28 ± 0.14	< 0.05
hsCRP (mg/L)	19.34 ± 2.41	2.96 ± 0.33	< 0.05
IL-6 (ng/L)	24.91 ± 2.63	9.84 ± 1.06	< 0.05
IL-8 (μg/L)	3.85 ± 0.41	0.78 ± 0.12	< 0.05
TNF-α (μg/L)	75.71 ± 12.48	20.44 ± 4.96	< 0.05
ICAM-1 (μg/L)	412.50 ± 56.40	147.60 ± 18.50	< 0.05
sCD40L (μg/L)	2.85 ± 0.35	1.14 ± 0.13	< 0.05

Table 3
Contents of serum β2-MG, inflammatory factors and adhesion molecules in patients with different severity of cerebral infarction.

Terms	Mild cerebral infarction	Moderate cerebral infarction	Severe cerebral infarction	P
β2-MG (mg/L)	1.77 ± 0.20	2.51 ± 0.30	3.98 ± 0.44	< 0.05
hsCRP (mg/L)	10.14 ± 1.14	17.22 ± 2.33	29.22 ± 3.47	< 0.05
IL-6 (ng/L)	15.04 ± 1.78	23.41 ± 2.97	34.01 ± 3.33	< 0.05
IL-8 (μg/L)	1.78 ± 0.22	2.97 ± 0.35	5.91 ± 0.68	< 0.05
TNF-α (μg/L)	43.14 ± 5.89	72.33 ± 9.41	101.33 ± 16.22	< 0.05
ICAM-1 (μg/L)	302.10 ± 34.80	401.20 ± 50.20	572.30 ± 68.70	< 0.05
sCD40L (μg/L)	1.77 ± 0.19	2.59 ± 0.29	4.47 ± 0.58	< 0.05

Table 4
Contents of serum β2-MG, inflammatory factors and adhesion molecules in patients with different volume of cerebral infarction.

Terms	Small volume of cerebral infarction	Medium volume of cerebral infarction	Large volume of cerebral infarction	P
β2-MG (mg/L)	1.69 ± 0.19	2.65 ± 0.32	3.85 ± 0.41	< 0.05
hsCRP (mg/L)	9.48 ± 1.14	16.87 ± 2.19	30.49 ± 3.68	< 0.05
IL-6 (ng/L)	14.27 ± 1.95	22.13 ± 2.62	33.28 ± 3.96	< 0.05
IL-8 (μg/L)	1.66 ± 0.22	3.15 ± 0.39	5.57 ± 0.61	< 0.05
TNF-α (μg/L)	40.39 ± 5.38	69.48 ± 9.68	95.65 ± 14.59	< 0.05
ICAM-1 (μg/L)	289.50 ± 32.60	389.40 ± 47.90	597.70 ± 71.40	< 0.05
sCD40L (μg/L)	1.89 ± 0.22	2.64 ± 0.31	4.18 ± 0.55	< 0.05

4. Discussion

Cerebral apoplexy is one of the three fatal diseases worldwide and also a common cause for long-term disability[13]. Cerebral apoplexy was divided into cerebral arterial thrombosis and hemorrhagic apoplexy, in which cerebral arterial thrombosis has a relatively high morbidity rate accounting for about 87% of cerebral apoplexy[14,15]. Cerebral arterial thrombosis, also known as cerebral infarction, is caused by hypoxia-ischemia brain injury. The physiopathologic mechanism involved in this damage process is very complex. Multiple inflammatory factors, adhesion molecules apoptotic molecules and oxidative stress molecules are all related to the ischemic injury of the brain tissue[16–19]. Inflammatory responses are considered as important changes of cerebral infarction throughout various pathologic stages.

Various inflammatory cells gather in the infarction and release a large number of inflammatory factors leading to brain tissue damage by microthrombus embolism, oxygen radical generation and endothelial cell damage, *etc.*[20,21]. The massive gathering of inflammatory cells will synthesize and secrete multiple inflammatory factors and chemotactic factor. Although the changes of the related cytokine contents in serum can provide values for disease assessment[22,23], the detection of single cytokine content in serum could not accurately evaluate the condition of disease because the changed cytokines in serum of different patients with cerebral infarction might be different.

In this study, β2-MG was selected to evaluate the disease severity for patients with acute cerebral infarction. At first, by analyzing the differences of contents of serum β2-MG between patients with acute cerebral infarction and healthy objects, we found that the content of serum β2-MG in patients with acute cerebral infarction was significantly elevated. Lymphocytes, neutrophile granulocytes, mononuclear macrophages and mesenchymal cells in bodies are the main source for β2-MG[24,25], while in the development process of acute cerebral infarction, the aggregation of multiple inflammatory cells in lesions can not only synthesize and secrete various inflammatory factors, and chemotactic factors, but also generate a lot of β2-MG. In addition, atherosclerosis is an important pathological character in patients with cerebral infarction. A large number of lymphocytes existing in the atheromatous plaque can induce the change of plaque characteristic and accelerate the progress of cerebral infarction. According to the analysis of the content of serum β2-MG, the severer cerebral infarction is, the greater infarct volume and the higher content of serum β2-MG will be. It can be concluded that the increase of the content of β2-MG is related to the occurrence and development of acute cerebral infarction and disease development. Combining the source of *in vivo* β2-MG, inflammatory reaction is the main approach for β2-MG to participate cerebral infarction.

Inflammatory factors are the most important cell factors for mediating inflammatory reactions. HsCRP is a acute phase protein, which increases rapidly after the occurrences of various acute inflammatory reactions, tissue damages, myocardial infarction, cerebral infarction, *etc*. Its content is positively correlated to the degree of inflammatory reaction. The mechanism of action of hsCRP are to activate the complement, induce the gathering of mononuclear macrophage and enhance vascular permeability and secretion of adhesion molecule, *etc.*[26]. TNF-α is a polypeptide cytokines secreted by activated mononuclear macrophage, which can directly damage the blood brain barrier, injury endothelial cells, increase the adhesion of inflammatory cells for vascular endothelial cell[27]. IL-6 and IL-8 are cytokines with multiple immune modulating functions and stronger chemotactic effect, which can increase the gathering of neutrophile granulocytes in the inflammatory site, induce the occurrence of degranulation, generate reactive oxygen metabolites and damage histocytes[28,29]. In the analysis of the content of inflammatory factors in serum, we found that the contents of serum hsCRP, IL-6, IL-8 and TNF-α increased obviously, and showed a positive correlation with the content of serum β2-MG, which suggested that the variation trend of the content of serum β2-MG was consistent with the changes of inflammatory factors contents, so that the degree of inflammatory reaction can be assessed by detecting the content of β2-MG.

In the progress of the activation and development of inflammatory reactions, apart from the inflammatory factors mentioned above, various adhesion molecules also play an important role in regulation. ICAM-1 is a glycoprotein on the membrane surface mediating cells and intercellular adhesion, cells and extracellular adhesion mechanisms. In the pathological process of cerebral infarction, the combination of ICAM-1 and ligand CD11a/CD18 can mediate the adhesion of hemameba in peripheral blood and vascular endothelial cells, penetrate vascular wall and infiltrate in the infarct area, and then aggravate inflammatory reaction of brain tissue. CD40L is a transmembrane glycoprotein of the complementary pairing with CD40. The combination of two substances can recruit various inflammatory cells and increase the secretion of inflammatory factors, tissue factors, and matrix metalloproteinase[30]. In the analysis of the content of adhesion molecules in serum, we found that the contents of serum ICAM-1 and sCD40L increased significantly, and showed a positive correlation with the content of serum β2-MG, which indicated that the variation trend of the content of serum β2-MG was consistent with the contents of inflammatory factors. Thus, it was further verified that the detection of the content of β2-MG can assess the degree of the inflammatory reaction.

In conclusion, the level of serum β2-MG was elevated abnormally in patients with acute cerebral infarction. The serum β2-MG level can assess the severity, infarction size and degree of inflammatory reaction in patients with acute cerebral infarction.

Conflict of interest statement

The authors report no conflict of interest.

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