Diagnostic Brain Medicine

CLINICAL RESEARCH

Study on the Relationship and Application of TNF-α, CRP, NGF and Cerebral Edema in Patients with Acute Cerebral Hemorrhage

Wangchao Dong[1, *] and Shanshan Wang[2, #]

[1]Nanjing hospital of Chinese Medicine Affiliated to Nanjing University of Chinene Medicine

[2]Department of Pharmacy, Children's Hospital of Nanjing Medical University, Nanjing, China

Keywords

Tumor necrosis factor-α, C-reactive protein, Nerve growth factor, Brain edema, Prognosis

Correspondence

Wangchao Dong, Nanjing hospital of Chinese Medicine Affiliated to Nanjing University of Chinene Medicine; Tel: 025-52276666

Received: 13 February 2020; Accepted: 19 March 2020; Published online: 18 April 2020

Diagnostic Brain Medicine 2020; 1(2): 38-43

Abstract

Objective To analyze the relationship between tumor necrosis factor-α, C-reactive protein, nerve growth factor and brain edema in patients with acute cerebral hemorrhage and its clinical application. **Methods** A total of 120 patients with acute cerebral hemorrhage who attended our hospital between April 2019 and May 2020 were enrolled. According to the severity of cerebral edema, the subjects were divided into mild, moderate, and severe group. The serum levels of TNF-α, CRP and NGF were measured and compared in the three groups. According to the prognosis, the subjects were divided into two groups, namely, the survival group and the death group. Spearman correlation was used to analyze the correlation between TNF-α, CRP and NGF levels and the severity of brain edema in patients. The diagnostic value of these three indicators was compared by the receiver operating curve and the area under curve. **Results** The levels of TNF-α, CRP and NGF in the moderate and severe groups were significantly higher than those in the mild group, and the levels of TNF-α, CRP and NGF in the severe group were noticeably higher than those in the moderate group. According to Spearman correlation analysis, serum levels of TNF-α, CRP and NGF were positively correlated with brain edema in patients with acute cerebral hemorrhage. The levels of TNF-α, CRP and NGF in the survival group were greatly lower than those in the death group. The AUC values of TNF-α, CRP and NGF were 0.860, 0.843 and 0.885, respectively, which showed high predictive performance for the prognosis of patients with acute cerebral hemorrhage. **Conclusion** The levels of TNF-α, CRP and NGF are closely related to the severity of cerebral edema in patients with acute cerebral hemorrhage, and these indicators are highly effective in evaluating the condition of cerebral edema in patients.

Introduction

Acute cerebral hemorrhage is a relatively common

type of cerebrovascular diseases, with a high disability rate and mortality rate [1]. Cerebral edema is the most serious complication of acute cerebral hemorrhage, and it is an important factor leading to the deterioration of the patient's condition [2]. Therefore, actively looking for indicators to determine the severity of cerebral edema in patients will effectively reduce the mortality of patients with acute cerebral hemorrhage. Studies have reported [2] that brain edema after acute cerebral hemorrhage is mainly related to increased permeability of the blood-brain barrier, inflammation, and abnormal ion channels. Tumor necrosis factor-α (TNF-α) is a biologically active cytokine produced by lymphocytes, etc. The change of TNF-α level can reflect the severity of inflammation and nerve function damage in the body [3]. Nerve growth factor (NGF) can maintain the homeostasis of the nervous system and is related to brain edema after cerebral hemorrhage to some extent [4]. Prevously, it has been found that C-reactive protein (CRP) gene is abnormally expressed in patients with acute cerebral hemorrhage, and can be used as an independent prognostic indicator [3]. At present, in clinical trials, there are few researches conducted on the relationship and application of TNF-α, CRP, NGF in determining the severity of cerebral edema in patients with acute cerebral hemorrhage. Therefore, this study investigated the relationship and application of TNF-α, CRP, NGF in determining the severity of cerebral edema in patients with acute cerebral hemorrhage. Related analyses were carried out, and the results are reported as follows.

Materials and methods

Clinical data

General information and data

The 120 patients with acute cerebral hemorrhage who came to our hospital for treatment between April 2019 and May 2020 were recruited as the research objects. According to the degree of cerebral edema, the research objects were divided into mild (edema <2cm) and moderate (edema ≤ 1/2 of the cerebral hemisphere) and severe (edema >1/2 of the cerebral hemisphere). In the mild group, there were 25 males and 16 females aging from 51 to 64 years, with an average age of (57.514.31) years old. In the moderate group, there were 23 males and 19 females, with an average age of (57.394.25) years old. 19 males and 18 females were in the severe group, with an average age of (56.884.42) years old. There was no statistically significant difference in the general clinical data between the three groups of the subjects (P>0.05), indicating that the data in this study were comparable. All the patients in this study signed an informed consent form, and the present study was approved by the hospital's Medical Ethics Committee.

Inclusion and exclusion criteria

Inclusion criteria: (1) The onset time was within 24 hours; (2) MRI or head CT showing cerebral hemorrhage; (3) Meeting the diagnostic criteria in the "*Guidelines for the Diagnosis and Treatment of Cerebral Hemorrhage in China*". Exclusion criteria: (1) Severe heart, liver and kidney dysfunctions; (2) Mental illness; (3) Coagulation dysfunction.

Methods

Treatment methods

After admission, all the subjects underwent head CT and routine examinations, and were given conventional treatments such as drugs for stopping bleeding, controlling blood pressure, reducing intracranial pressure, and protecting nerves.

Detection method

From all the subjects, 5 mL of fasting blood in the morning was collected into a blood collection tube, centrifuged at a high speed to separate the serum and stored at -20°C for later testing. The enzyme-linked immunosorbent kit provided by Wuhan Yunclone Technology Co., Ltd. was used to detect TNF-α, CRP, and NGF strictly following the instructions.

Prognosis

All the study subjects were followed up from admission to discharge, and were divided into two groups according to their prognosis. There were 15 patients in the dead group, while 105 patients in the

survival group.

Statistical analysis

SPSS 21.0 was used for statistical analysis. The count data were compared by χ2 test, and the measurement data were shown by mean ± standard deviation（$\bar{x}$±s). Comparison between two groups was analyzed by t-test, while comparison between three groups was analyzed by F analysis of variance, three-group comparison was conducted using LSD-t test was used for pairwise comparison. The correlation between TNF-α, CRP, NGF and the severity of cerebral edema was analyzed by Spearman correlation test. The predictive performance of TNF-α, CRP, and NGF on patient prognosis was evaluated based on receiver operating curve (ROC) Area (AUC), which means that an AUC value between 0.5 and 0.7 indicates a low predictive performance, an AUC value between 0.7 and 0.9 indicates a moderate predictive performance, and an AUC value above 0.9 indicates a high predictive value. A P<0.05 was considered as a statistical difference.

Results

Comparison of the levels of TNF-α, CRP and NGF in the three groups

The levels of TNF-α, CRP and NGF in the moderate and severe groups were significantly higher than those in the mild group (P<0.05). Moreover, the levels of TNF-α, CRP and NGF in the severe group were obviously higher than those in the moderate group (P<0.05), see Table 1.

Table 1 Comparison of the levels of TNF-α, CRP and NGF levels in the three groups（$\bar{x}$±s）

Groups	Cases	TNF-a（pg/mL）	CRP（pg/mL）	NGF（mg/mL）
Mild group	41	46.31±9.57	7.95±0.81	4.71±1.18
Moderate group	42	71.42±12.36[a]	9.51±0.92[a]	7.34±1.49[a]
Severe group	37	94.51±14.29[ab]	11.08±1.18[ab]	11.26±2.12[ab]
F		187.535	93.000	278.108
P		0.000	0.000	0.000

Note: Compared with the mild group, [a]P<0.05; compared with the moderate group, [b]P<0.05.

Correlation study of TNF-a, CRP, NGF and cerebral edema severity

Spearman correlation analysis showed that the serum levels of TNF-α, CRP, NGF in the patients with acute cerebral hemorrhage were positively correlated with the severity of cerebral edema (P<0.05), see Table 2, Figure 1.

Table 2 Correlation study of TNF-α, CRP, NGF and cerebral edema severity

Factors	Cerebral edema severity	
	r	*P*
TNF-a	0.882	0.000
CRP	0.800	0.000
NGF	0.914	0.000

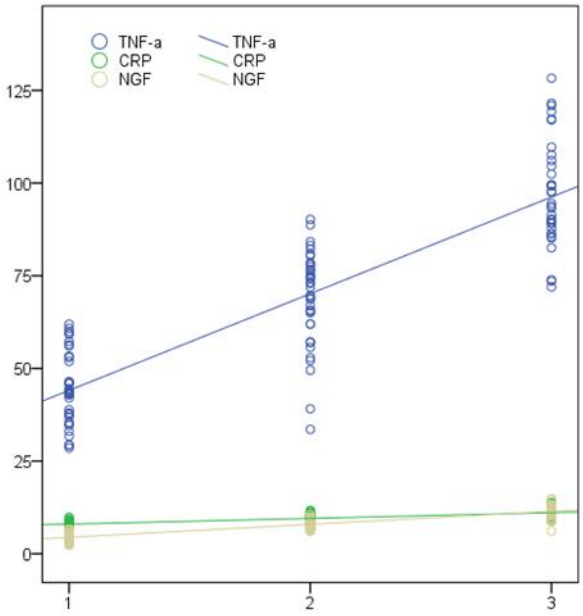

Figure 1 Spearman correlation analysis of TNF-α, CRP, NGF and cerebral edema severity ("1" is mild; "2" is moderate; "3" is severe)

Comparison of TNF-α, CRP and NGF levels between the survival group and the death group

The levels of TNF-α, CRP and NGF in the survival group were significantly lower than those in the death group (P<0.05), see Table 3.

Table 3 Comparison of TNF-α, CRP and NGF levels between the survival group and the death group ($\bar{x}\pm s$)

Groups	Cases	TNF-a（pg/mL）	CRP（pg/mL）	NGF（mg/mL）
The survival group	105	72.62±10.11	9.41±0.82	8.41±1.34
The death group	15	109.57±9.63	12.26±1.21	12.03±1.25
t		-13.314	-11.795	-9.863
P		0.000	0.000	0.000

The prognostic prediction of TNF-α, CRP, and NGF levels

The AUC values of TNF-α, CRP, and NGF were 0.860, 0.843, and 0.885, respectively, all of three indicators showed a high predictive performance for the prognosis of patients with acute cerebral hemorrhage, see Table 4, Figure 2.

Table 4 The prognostic prediction of TNF-α, CRP, and NGF levels

Variations	AUC	SE	95%*CI*
TNF-a	0.860	0.0628	0.785~0.917
CRP	0.843	0.0627	0.766~0.903
NGF	0.885	0.0700	0.814~0.936

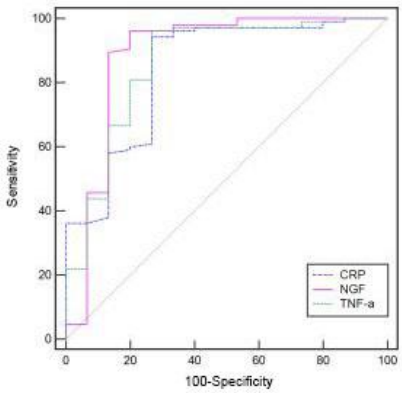

Figure 2 ROC curves of TNF-α, CRP, NGF on predicting the prognosis of patients with acute cerebral hemorrhage

Discussion

Acute cerebral hemorrhage is the most deadly type of stroke, and its incidence increases with the aging of the population. Cerebral edema after cerebral hemorrhage, which is a determinant of clinical deterioration, seriously threatens the life and health of patients [5]. The formation of cerebral edema can occur within a few hours after cerebral hemorrhage and will last for a period of time. The highly complicated development process of acute cerebral hemorrhage is related to hematoma, blood clot retraction, coagulation cascade reaction, thrombin formation, red blood cell lysis, and the toxicity of hemoglobin and its degradation products [2]. Cerebral edema may cause the interruption of potassium ion channels and sodium ion channels, leading to a series of adverse effects such as damage to nerve function, aggravation of inflammation, and increased intracranial pressure [3, 6]. Therefore, timely determination of the severity of cerebral edema in clinical practice plays an important role in the effective treatment of patients with acute cerebral hemorrhage.

Studies have reported [2] that TNF-α is a predictor of acute cerebral hemorrhage and plays an important role in local inflammation and thrombosis pathways. Increased levels of TNF-α in the patients with acute cerebral hemorrhage are related to the severity of cerebral edema, deterioration of early neurological function and increased mortality [5]. Study conducted by Lin et al showed that the level of TNF-α in patients with acute cerebral hemorrhage was significantly higher than that of healthy individuals, and it was significantly positively correlated with the severity of the disease [7]. In this study, it was found that as the severity of brain edema in patients was significantly positively related to the level of TNF-α, and such a result is consistent with previous studies [7]. Moreover, we also determined the level of TNF-α I both the survival group and the death group. The results showed that the TNF-α level of the survival group was significantly lower than that of the death group, indicating that the TNF-α level can serve as an effective indicator to evaluate the patient's condition. CRP is a pro-inflammatory cytokine that participates in the inflammatory response and coagulation process by activating the fibrinolytic system and the complement system, and is related to the prognosis of cerebral hemorrhage [8]. Noticeably, such a finding was also observed in our study, as in our study, the level of CRP in the patients with severe cerebral edema was significantly higher than those with mild cerebral edema, and the CRP level of the survival group was significantly lower than that of the death group. Nozoe et al. [9] studied the relationship between changes in quadriceps thickness and CRP level after acute stroke, and found that the thickness of quadriceps femoris in CRP-positive patients decreased more than those with non-paralyzed limbs and CRP-negative patients, indicating that CRP positive and CRP level are significantly correlated with the prognosis after acute stroke. NGF [10] is a nerve growth factor that affects the survival and growth of neurons in the process of nerve injury, and the level of

NGF may be a predictor of the severity and prognosis of traumatic brain injury. Our study showed that the NGF level of the survival group was significantly lower than that of the death group, and that the NGF level increased with the aggravation of cerebral edema of the patients, proving that NGF can be used as an indicator of the cerebral edema of patients with acute cerebral hemorrhage. Spearman correlation analysis demonstrated that the severity of cerebral edema in the patients with acute cerebral hemorrhage was noticeably positively correlated with the serum levels of TNF-α, CRP and NGF, indicating that the above indicators were predictive of the clinical diagnosis of cerebral edema in the patients with acute cerebral hemorrhage.

Previous studies have shown [11] that the serum levels of TNF-α, CRP and other inflammatory factors in patients with cerebral hemorrhage are closely related to the prognosis and severity of the disease. Cho et al. [10] explored the neurogenic voiding dysfunction caused by cerebral hemorrhage in a rat model, and found that compared with the control rats, the expressions of c-Fos and NGF in the neuronal voiding center of the rats were greatly up-regulated with the induction of cerebral hemorrhage. In this study, we used the ROC curve to compare the predictive performance of TNF-α, CRP, and NGF for the prognosis of patients with acute cerebral hemorrhage. The results showed high AUC values of the above three indicators, suggesting TNF-α, CRP, NGF are highly predictive of the prognosis of patients with acute cerebral hemorrhage.

In summary, the levels of TNF-α, CRP, and NGF in patients with acute cerebral hemorrhage are positively correlated with the severity of cerebral edema, and these three indicators are predictive of the prognosis of patients with acute cerebral hemorrhage.

Declaration of conflict-of-interest

The authors declare no conflict-of –interest.

References

[1] Wilkinson, D.A., Pandey, A.S., Thompson, B.G., et al. Injury mechanisms in acute intracerebral hemorrhage. Neuropharmacology, 2018, 134(Pt B): 240-248.

[2] Cai, M., Yu, Z., Wang, L., et al., Tongxinluo reduces brain edema and inhibits post-ischemic inflammation after middle cerebral artery occlusion in rats. J Ethnopharmacol, 2016. 181: p. 136-45.

[3] Bernstein, J.E., P. Savla, F. Dong, et al. Inflammatory Markers and Severity of Intracerebral Hemorrhage. Cureus, 2018, 10(10): e3529.

[4] Patterson, S.L., M.S. Grady, M. Bothwell. Nerve growth factor and a fibroblast growth factor-like neurotrophic activity in cerebrospinal fluid of brain injured human patients. Brain Res, 1993. 605(1): 43-49.

[5] Wilkinson, D.A., Pandey, A. S., Thompson, B. G.,et al., Injury mechanisms in acute intracerebral hemorrhage. Neuropharmacology, 2018. 134(Pt B): p. 240-248.

[6] Ran, Y.H. and H. Wang, Iptakalim, an ATP-sensitive potassium channel opener, confers neuroprotection against cerebral ischemia/reperfusion injury in rats by protecting neurovascular unit cells. J Zhejiang Univ Sci B, 2011. 12(10): p. 835-45.

[7] Lin, C., Tang, X., Shi, Z., et al., Serum tumor necrosis factor alpha levels are associated with new ischemic brain lesions after carotid artery stenting. J Vasc Surg, 2018. 68(3): p. 771-778.

[8] Bernstein, J.E., Savla, P., Dong, F., et al., Inflammatory Markers and Severity of Intracerebral Hemorrhage. Cureus, 2018. 10(10): p. e3529.

[9] Nozoe, M., Kanai, M., Kubo, H., et al., Changes in Quadriceps Muscle Thickness, Disease Severity, Nutritional Status, and C-Reactive Protein after Acute Stroke. J Stroke Cerebrovasc Dis, 2016. 25(10): p. 2470-4.

[10] Cho, Y.S., Ko, I. G., Kim, C. J., et al., A novel intracerebral hemorrhage-induced rat model of neurogenic voiding dysfunction: Analysis of lower urinary tract function. Mol Med Rep, 2015. 12(2): p. 2563-9.

[11] Ziai, W.C. and J.R. Carhuapoma, Intracerebral Hemorrhage. Continuum (Minneap Minn), 2018. 24(6): p. 1603-1622.