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Original Article

Correlations of IL-10 concentrations in serum and hematoma fluid with brain edema and hematoma volumes in patients with acute cerebral hemorrhage

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Abstract: Objective: To explore the concentrations of IL-10 in patients with acute cerebral hemorrhage (ACH) and the correlation of IL-10 and perihematomal cerebral edema. Methods: Sixty patients with ACH admitted to our hospital from January 2014 to June 2017 were divided into the <6 h group, the 6-12 h group and the 12-24 h group. Forty concomitant healthy persons were included in the control group. The concentrations of IL-10 in serum and in intracranial hematoma were compared among the ACH patients with the use of enzyme linked immunosorbent assay (ELISA). Additionally, the volume of cerebral hemorrhage and edema of ACH patients were compared by CT scan across the groups according to the Coniglobus formula, and Pearson correlation analysis was used to clarify the correlations of IL-10 with the volume of cerebral edema and hemorrhage. Results: The concentrations of IL-10 in serum and hematoma fluid in patients with ACH increased more significantly than the controls (P<0.001). The IL-10 concentrations showed a rising trend overt time within 24 hours after ACH onset. There was no significant difference in the concentrations of IL-10 in serum and hematoma fluid between the <6 h group and the control group. However, the concentrations of IL-10 were significantly higher in the 6-12 h and 12-24 h groups than in the control groups, and higher than that of the <6 h group. There was a substantial disparity in the concentrations of IL-10 between the 6-12 h group and the 12-24 h group (all P<0.001). There were insignificant differences in the volume of intracerebral hemorrhage among patients at different phases of ACH, but the volume of edema in peripheral cerebral tissue after hematoma showed a rising trend. There were significant differences in the volume of edema across the groups (all P<0.001). The volume of intracerebral hemorrhage in patients with ACH was not correlated with the concentrations of IL-10 in serum and in hematoma at different phases, but the volume of edema was positively correlated between the concentrations of IL-10 at different phases. There were positive correlations between the IL-10 concentrations in serum and those in hematoma at different phases. Conclusion: The IL-10 concentrations in patients with ACH increase over time and show dynamic changes. There is a positive correlation of IL-10 with the volume of perihematomal cerebral edema.

Keywords: Acute cerebral hemorrhage, cerebral edema, IL-10, correlation

Introduction

Acute cerebral hemorrhage (ACH) is an acute cerebrovascular disease with an acute onset, as well as high disability and mortality rates, which seriously threatens the physical and mental health of patients [1, 2]. In addition to acute space-occupying compression of the perihematomal cerebral tissue, cerebral edema after hematoma can also lead to further damage to brain cells, aggravating the patient's condition; it is one of the key factors for exacerbation of the conditions of patients with cerebral hemorrhage [3]. Studies have reported secondary injury of perihematomal cerebral edema following ACH is a fundamental factor for deterioration of neurological function in patients [4, 5]. How to effectively prevent and treat perihematomal cerebral edema after ACH is so important that it is attracting increasing attention from relevant scholars.

Cytokines, a population of small molecular peptides with immune activity, regulate or mediate

inflammation. Recent studies have revealed that cytokine-mediated inflammation plays a decisive role in the secondary injury of brain edema after intracerebral hemorrhage [6, 7]. The vast majority of previous studies have focused on pro-inflammatory factors such as IL-4, IL-6 and IL-8 [8, 9]. The effects of anti-inflammatory factors in cerebral edema formation after intracerebral hemorrhage are rarely reported. IL-10 is a key anti-inflammatory factor, mainly generated by lymphocytes and mononuclear macrophages, which can effectively inhibit the activity and synthesis of some cytokines [10, 11]. A study found IL-10 significantly reduced the volume of cerebral infarction and severity of cerebral edema [12]. A prospective study reported that IL-10 had a preventive effect on the occurrence of cerebral hemorrhagic stroke. The lower the expression of serum IL-10 is, the higher the rates of morbidity and mortality of cerebral hemorrhagic stroke [13]. Therefore, in this study, the clinical data of 60 patients with ACH were retrospectively analyzed to further investigate the role of IL-10 in the development of cerebral edema after ACH, with an expectation to bring some new insights for the treatment of ACH.

Materials and methods

Data collection

General information: Sixty patients with ACH admitted to our hospital from January 2014 to June 2017 were enrolled as the study subjects, and 40 healthy people were included in the control group. Inclusive criteria for patients with ACH were: (1) patients older than 18 years met the diagnostic criteria for ACH, as demonstrated cerebral hemorrhage by cranial CT and MRI which did not invade into the ventricles; (2) the first onset with the course of the disease less than 24 hours; (3) the respiratory and circulatory functions of the patients remained stable; (4) patients actively complied with the study [14]. Exclusion criteria: (1) patients with severe multiple organ dysfunction present in the heart, liver, kidney and other important organs; (2) transient ischemic attack, stroke or brain injury in the previous three months; (3) patients with coagulation dysfunction, cerebral vascular malformations or cerebral hemorrhage caused by vasculitis; (4) patients with malignant tumors; (5) a history of acute or chronic infection in the previous month. This study got approval from the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine, and the relatives or guardians of the enrolled patients signed written informed consent.

Outcome measures

Patients with ACH were randomized into three groups in terms of the onset time: <6 h group (n=12), 6-12 h group (n=28) and 12-24 h group (n=20). The concentrations of IL-10 in serum of patients with ACH were compared at different time phases. Venous blood (3 ml) was drawn from elbow vein of each patient in all the groups, placed in an anticoagulant tube, and centrifuged for 10 min at 2500 r/min. Supernatants were collected and stored in a tube at -20°C. The concentrations of IL-10 in serum of patients in each group were detected strictly according to the instructions with the use of the Enzyme linked immunosorbent assay (ELISA). The ELISA kits were purchased from R&D Science, USA.

The concentrations of IL-10 in hematoma fluid of patients were compared among the groups. Upon admission, the patients with ACH underwent cerebral puncture or evacuation of intracranial hematoma, and samples of hematoma fluid were collected. The IL-10 concentrations in hematoma fluid of patients with ACH were tested by ELISA within 6 hours, 6-12 hours and 12-24 hours after intracerebral hemorrhage.

Intracerebral hemorrhage and perihematomal cerebral edema volumes were compared among all the groups in different phases. All patients underwent cranial CT examination upon admission. Intracerebral hemorrhage volume was calculated according to the Coniglobus formula, i.e. the volume of intracerebral hemorrhage equals to $1/6\pi \times A \times B \times C$, in which A denotes the longest diameter of hematoma in the maximum hematoma area, B denotes the longest diameter perpendicular to the longest diameter in the maximum hematoma area, and C denotes the number of bleeding areas on CT scan. The brain edema showed in the low density area around the hematoma on CT scan. According to the Coniglobus formula, the volume of edema around the hematoma was calculated as follows: Edema volume = (Cerebral hemorrhage volume + volume in the low density area around the hematoma) - Cerebral hemorrhage volume.

Table 1. Basic data of patients in all the groups

Variable	<6 h group	6-12 h group	12-24 h group	Control group	F/χ^2 value	*P* value
Case	12	28	20	40		
Male/Female (n)	8/4	19/9	11/9	25/15	0.906	0.824
Age (year)	56.7±4.8	57.2±5.4	57.7±5.8	58.4±6.1	0.256	0.857
BMI (Kg/m^2)	23.4±0.8	23.6±0.9	23.9±1.0	23.7±0.9	0.846	0.472
Hypertension (n)	7	10	9	17	1.794	0.616
Diabetes (n)	4	6	5	8	1.011	0.798
Hyperlipemia (n)	6	8	7	12	2.016	0.569
Renal insufficiency (n)	3	5	4	7	0.376	0.945

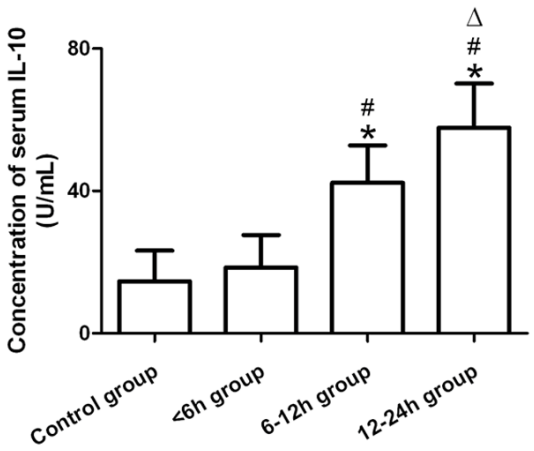

Figure 1. IL-10 concentration in serum of each group. *P<0.001 for comparison with the control group; #P<0.001 for comparison with the <6 h group; ΔP<0.001 for comparison with the 6-12 h group.

Statistical analysis

SPSS software, version 19.0 was applied to process all the data. Measurement data with normal distribution are described as mean ± standard deviation. Inter-group comparisons were made using the one-way ANOVA followed by a post-hoc Bonferroni test. Count data are expressed as percentage. Between-group comparisons were made by partitioning Chi-square tests, and the correlations between IL-10 and cerebral hemorrhage and edema volumes were analyzed by Pearson correlation analysis. P<0.05 was set to significantly different.

Results

Basic data of patients

Patient gender, age, body mass index (BMI) and history of hypertension were well-matched among the ACH groups (including the <6 h group, 6-12 h group, and 12-24 h group), and the control group (**Table 1**).

IL-10 concentrations in serum of each group

The concentrations of IL-10 in serum of patients with ACH increased significantly compared with the controls (P<0.001). With the increase in onset time, the concentrations of IL-10 in serum showed a rising trend. No significant difference was noted in the concentrations of IL-10 in serum between the <6 h group and the control group (P=0.179). The concentrations of IL-10 in serum of the 6-12 h and 12-24 h groups were significantly higher than that of the control group (both P<0.001). Additionally, significant between-group difference was observed among the <6 h group, the 6-12 h group and the 12-24 h group (P<0.001; **Figure 1**).

IL-10 concentrations in hematoma fluid of patients with ACH at different phases

The IL-10 concentration in hematoma fluid of the patients with ACH was significantly higher than that of the controls (P<0.001). The IL-10 concentrations in hematoma fluid at different phrases were considerably different among the patients with ACH (all P<0.001). The IL-10 concentrations in hematoma fluid of the 6-12 h and 12-24 h groups were substantially higher compared with that of the control group (both P<0.001). The values of the IL-10 concentrations showed a rising trend within 24 hours after the onset of cerebral hemorrhage (**Figure 2**).

Intracerebral hemorrhage and edema volumes among patients with ACH at different phrases

The volume of cerebral hemorrhage in patients with ACH in the <6 h, 6-12 h and 12-24 h groups were 34.8 (±8.5 mL), 36.4 (±9.0 mL) and 39.1

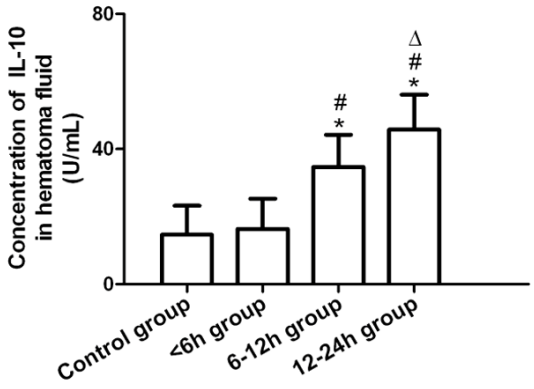

Figure 2. IL-10 concentration in hematoma fluid of each group. *P<0.001 for comparison with the control group; #P<0.001 for comparison with the <6 h group; ΔP<0.001 for comparison with the 6-12 h group.

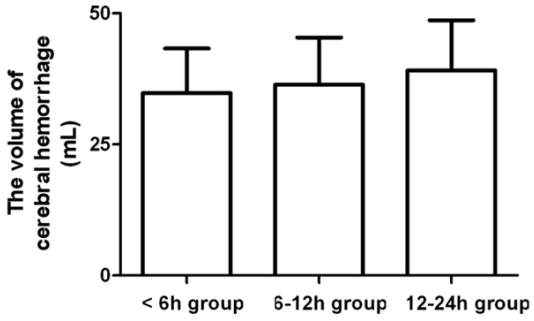

Figure 3. Volume of intracerebral hemorrhage at different phases in patients with ACH.

Table 2. Edema volume in patients with ACH at different phases

Variable	Edema volume (mL)
<6 h group	2.1±0.6
6-12 h group	5.6±1.7*
12-24 h group	12.5±6.6*,#
F value	39.18
P value	<0.001

Note: *P<0.001 for comparison with the <6 h group; #P<0.001 for comparison with the 6-12 h group.

(±9.6 mL), respectively. There were insignificant differences in cerebral hemorrhage volume among the groups (F=0.941, P=0.396; **Figure 3**).

Edema volume of patients with ACH in the <6 h, 6-12 h and 12-24 h groups were 2.1 (±0.6 mL), 5.6 (±1.7 mL) and 12.5 (±6.6 mL), respectively. Significant differences in edema volume were seen among the groups (P<0.001; **Table 2**).

Correlations of IL-10 with intracerebral hemorrhage and edema volumes in patients with ACH

Pearson correlation analysis revealed that the volume of cerebral hemorrhage in patients with ACH was not correlated with the IL-10 concentrations in serum and hematoma fluid at different phases, but edema volume was positively correlated with the IL-10 concentrations in serum and hematoma fluid (**Tables 3** and **4**). In addition, the IL-10 concentrations in serum at different phases were positively correlated with the IL-10 concentrations in hematoma fluid (**Table 5**).

Discussion

Cerebral edema after intracerebral hemorrhage is the most common pathophysiological changes in patients with ACH, and also a main cause of secondary brain injury. Relevant literature indicates infiltration of inflammatory cells occur after intracerebral hemorrhage, and released multiple cytokines induce injuries to vascular endothelial cells, resulting in cytotoxic cerebral edema, which further aggravates the permeability of the blood-brain barrier and ultimately leads to vascular cerebral edema [15, 16]. Cerebral edema after intracerebral hemorrhage closely relates to prognosis of patients and is the key pathological basis for disability and deaths of ACH patients [17]. Currently, the pathogenesis of cerebral edema after cerebral hemorrhage still remains unknown, which greatly limits the treatment of patients with cerebral hemorrhage.

IL-10, an acidic protein composed of two homologous subunits with the molecular weight ranging from 35 to 40KD, is a potent immunosuppressive and inflammatory inhibitor. IL-10 suppresses many steps of inflammation [18, 19]. A study reported IL-10 reduced the synthesis and activity of pro-inflammatory factors such as IL-6, IL-1 and TNF-α, and the expression of matrix metalloproteinases by inhibiting gene transcription [20]. Other studies have demonstrated IL-10 plays a role in the protection of neuronal brain tissue, as it can inhibit synthesis of nitric oxide synthase, and regulate the sensitivity of neurons to toxicity of excitatory amino acid as well as apoptotic protein in cerebrospinal fluid [21-23]. Protti et al. argued that IL-10 could suppress the development of atherosclerosis, reduce neuronal injuries and death after

Table 3. Correlations of IL-10 in serum with cerebral hemorrhage and edema volume in patients with ACH

Parameter	Cerebral hemorrhage volume		Edema volume	
	r value	*P* value	r value	*P* value
IL-10 in serum at <6 h	0.200	0.051	0.708	0.003
IL-10 in serum at 6-12 h	0.198	0.065	0.787	<0.001
IL-10 in serum at 12-24 h	0.187	0.079	0.802	<0.001

Table 4. Correlations of IL-10 in hematoma fluid with cerebral hemorrhage and edema volume in patients with ACH

Parameter	Cerebral hemorrhage volume		Edema volume	
	r value	*P* value	r value	*P* value
IL-10 in hematoma fluid at <6 h	0.147	0.106	0.685	0.004
IL-10 in hematoma fluid at 6-12 h	0.165	0.084	0.714	0.002
IL-10 in hematoma fluid at 12-24 h	0.154	0.092	0.731	0.001

Table 5. Correlation between IL-10 in serum and IL-10 in hematoma fluid

Parameter	IL-10 in hematoma fluid	
	r value	*P* value
IL-10 in serum at <6 h	0.663	0.005
IL-10 in serum at 6-12 h	0.761	<0.001
IL-10 in serum at 12-24 h	0.790	<0.001

cerebral ischemia, and promote the preclusion of inflammatory response in many aspects [24]. Nevertheless, there are few reports about the expression and effects of IL-10 in cerebral edema after intracerebral hemorrhage. The findings of this study revealed that the IL-10 concentrations in serum and hematoma fluid in patients with ACH were significantly higher than those of the healthy controls. In patients with ACH, no significant difference was noted in the IL-10 concentrations in serum and in hematoma fluid of the <6 h group relative to those of the control group, but the IL-10 concentrations of the 6 h-12h and 12h-24h groups were significantly higher than those of the <6 h group and the control groups. Moreover, significant higher IL-10 concentrations of patients were observed in the 12h-24h group versus the 6 h-12h group. This suggests that IL-10 is a decisive cytokine in the inflammatory response during the onset and development of cerebral hemorrhage. The IL-10 concentration shows an ongoing increase at 24 hours after onset of cerebral hemorrhage. This may be related to the great number of inflammatory factors generated after ACH, which induces compensatory release and secretion of more endogenous anti-inflammatory mediators against their effects. This is largely consistent with the results reported by Zhou et al. [25]. This study implies that the expression of IL-10 in serum and intracranial hematoma fluid may be associated with the inflammation induced by neuroendocrine dysfunction after intracerebral hemorrhage, and the differences in IL-10 concentrations in serum and intracranial hematoma fluid may be attributed to the differences in the magnitude and feedback of inflammation induced by inflammatory factors expression and stress response in the lesions of intracerebral hemorrhage.

The findings of this study indicated that there was no correlation between the elevation of IL-10 concentration and cerebral hemorrhage volume. It may be due to the correlation between IL-10 concentration and the pathophysiological changes after cerebral hemorrhage, which is generally consistent with the findings reported by Garcia et al. [26]. Wang et al. reported that elevated IL-10 levels were associated with recurrent hemorrhage within 24 hours in patients with intracerebral hemorrhage [27]. Wu et al. held that larger volume of cerebral edema implies higher pressure of brain tissue and more severe injury [28]. Our current study showed that within 24 hours after ACH, cerebral edema volume in patients increased gradually with the onset time; there was a positive correlation between the increase of IL-10 concentrations and the volume of cerebral edema in patients with ACH. This indicates IL-10 can reflect the severity of the disease, which may be related to the destruction of microvascular integrity in the lesions and activation of vascular endothelial cells [29].

In summary, inflammatory response is implicated in the onset and development of cerebral edema after cerebral hemorrhage. The IL-10 concentrations in serum and intracranial hematoma fluid of patients with ACH increase significantly, and the increase in IL-10 concentration

is positively correlated with cerebral edema volume after cerebral hemorrhage. However, there are still some limitations in this study, such as a small sample size, single-center, and research only on the changes in IL-10 concentration within 24 hours after intracerebral hemorrhage. Additionally, the mechanisms regarding how IL-10 is involved in the onset and development of cerebral edema after ACH are unclear. In future research, additional multi-center studies with a larger sample size are required to observe the changes in IL-10 concentration beyond 24 hours after intracerebral hemorrhage and further delve into the effects of IL-10 in cerebral edema formation after intracerebral hemorrhage.

Disclosure of conflict of interest

None.

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