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Expressions of serum inflammatory cytokines and their relationship with cerebral edema in patients with acute basal ganglia hemorrhage

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Abstract. – OBJECTIVE: The aim of the present study is to investigate expressions of inflammatory cytokines and their relationship with cerebral edema in the patients with acute basal ganglia hemorrhage.

PATIENTS AND METHODS: Between January 2015 and March 2016, 94 patients with acute basal ganglia hemorrhage admitted to our institution were included in the present study. Serum levels of interleukin (IL)-4, IL-6, IL-8 and IL-10 were measured using enzyme-linked immunosorbent assay (ELISA), and conditions of cerebral edema were evaluated using head CT upon admission, 1d after admission and 3d after admission, respectively.

RESULTS: Serum levels of IL-4, IL-6 and IL-8 peaked 1d after admission and decreased 3d after admission with statistical significance (p <0.05); the IL-10 level was continuously increased after admission and peaked 3 days after admission with statistical significance (p<0.05). Cerebral edema was not observed in any of these patients upon admission, while occurred with a maximal edema volume 1 day after admission and the volume decreased 3 days after admission with statistical significance (p <0.05). Correlation analysis showed that levels of IL-4, IL-6 and IL-8 were positively correlated with severity of cerebral edema (r=0.324, 0286, 0.305, p <0.05 respectively), whereas IL-10 level was negatively correlated with severity of cerebral edema (r=-0.336, p <0.05).

CONCLUSIONS: Serum levels of IL-4, IL-6 and IL-10 are positively correlated while the IL-10 level is negatively correlated with the severity of the cerebral edema in patients with acute basal ganglia hemorrhage.

Key Words: Acute basal ganglia haemorrhage, Inflammatory cytokines, Cerebral edema, Correlation.

Introduction

Intracerebral hemorrhage (ICH) refers to the bleeding resulted from the rupture of blood vessels in the brain parenchyma caused by non-traumatic injury, resulting in a mortality of 30%-40% in the acute phase of the disease[1]. Acute ICH (AICH), as a commonly seen condition in clinical settings, is mainly associated with hyperlipidemia, diabetes mellitus, hypertension, aging of blood vessels and other cerebral vascular diseases. Emotional stress and strenuous physical exertion are two common triggers of AICH, which is featured by abrupt onset and high mortality at the early stage of the disease. Perihematomal edema (PHE) associated with AICH is an important event that leads to persistent aggravation of conditions in patients[2,3]. Post-AICH cerebral edema can induce the massive release of inflammatory cytokines, which in turn, are involved in the development of PHE and lead to further exacerbation of patient conditions, significantly affecting the prognosis of the disease[4,5]. Post-AICH inflammatory response is more severe than hemorrhagic injury in that infiltration of neutrophils occurs shortly after the onset of AICH. These neutrophils can release a variety of cytokines, including interleukin (IL)-4, IL-6, IL-8, IL-10 and tumor necrosis factor (TNF), aggravating brain damage[6,7]. In the present study, clinical data of 94 patients with AICH in the basal ganglia were analyzed to investigate the relationship between the expression of inflammatory cytokine and cerebral edema in these patients.

Patients and methods

Patients

Between January 2015 and March 2016, 94 patients with acute basal ganglia hemorrhage admitted to our institution were included in the

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present study. All these patients met ICH diagnostic criteria addressed in the Key Facts in the Diagnosis of Various types of Cerebrovascular Diseases[8]. The inclusion criteria are as follows: systolic blood pressure < 200 mmHg, diastolic blood pressure <120 mmHg, head CT confirmed the hemorrhagic site at the basal ganglia with a hemorrhagic volume of < 30 ml and the ventricle not affected. The following exclusion criteria were considered: patients with unstable circulatory and respiratory functions, death within 72h of onset, severe co-morbidities of vital organs including the liver, the heart and the kidney, severe and primary co-morbidities of the hematopoietic system and the endocrine system, ear vertigo, hypoglycemia, cervical spine disorder, sick sinus syndrome, vascular syncope, traumatic ICH, non-basal ganglia hemorrhage, arteriovenous malformation and tumor bleeding. Eventually, 94 patients were enrolled, including 52 males and 42 females with an age range of 41-70 years and a mean age of 55.81±5.91 years. This study was approved by the Ethics Committee of our institution and written informed consent was obtained from all patients or families.

Outcome Measures

Five milliliters of fasting venous blood were collected from the cubital vein of all patients at 7 am-9 am upon admission, 1d after admission and 3d after admission, respectively. Blood samples were centrifuged at 3000 rpm for 10 min, serum isolated and stored at -80°C. Serum levels of IL-4, IL-6, IL-8 and IL-10 were measured using enzyme-linked immunosorbent assay (ELISA) by following manufacturer's instructions (Flarebio Biotech LLC, Wuhan, China). Conditions of cerebral edema were evaluated using head CT upon admission, 1 day after admission and 3d after admission, respectively. The volume of hematoma was calculated using the following formula: hematoma volume = length × width × number of slices × slice thickness (1 cm) × π / 6. In this formula, length and width represent the ones of the largest are of hemorrhage and number of slices represents a total number of CT slices comprising hematoma. The volume of cerebral edema was calculated using the similar method by selecting hemorrhagic slices containing edema, measuring the length and width and calculating volume of the entire lesion. Subsequently, the volume of edema was calculated using the following formula: volume of cerebral edema = volume of entire lesion – hematoma volume.

Statistical Analysis

Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Qualitative data were expressed as n (%) and analyzed using χ^2 test. Quantitative data were expressed as (X±S) and analyzed using t-test. Pearson's correlation was employed to analyze the correlation between data. p <0.05 was considered statistically significant.

Results

Serum Levels of Inflammatory Cytokines

Serum levels of IL-4, IL-6, IL-8 and IL-10 were significantly increased 1d after admission (p<0.05). Of these, levels of IL-4, IL-6, IL-8 peaked at 1 day after admission and decreased at 3 days after admission with statistical significance (p<0.05); however, levels of IL-10 peaked at 3 days after admission with statistical significance (p<0.05) (Table I).

Conditions of Cerebral Edema

Cerebral edema was not observed in any of these patients upon admission. However, cerebral edema occurred with a maximal edema volume of (19.36±6.12) ml 1 day after admission but decreased to a volume of (14.72±4.23) ml 3d after admission with statistical significance (p <0.05).

Table I. Serum levels of inflammatory cytokines at different time points.

Time points	IL-4 (ng/L)	IL-6 (ng/L)	IL-8 (ng/L)	IL-10 (ng/L)
Upon admission (T0)	41.75±10.86	74.36±14.48	41.87±13.72	25.33±7.42
1d after admission (T1)	63.31±18.46	92.26±21.64	66.15±21.36	60.28±17.89
3d after admission (T3)	53.27±17.13	83.33±18.47	53.29±17.45	95.35±24.54
t(T1:T0)/p	9.760/0.000	6.665/0.000	9.273/0.000	17.496/0.000
t(T3:T0)/p	5.507/0.000	3.706/0.000	4.988/0.000	26.480/0.000
t(T3:T1)/p	-3.865/0.000	-3.043/0.001	-4.520/0.000	11.196/0.000

Correlation Between Inflammatory Cytokines and Cerebral Edema

Pearson's correlation analysis revealed that levels of IL-4, IL-6 and IL-8 were positively correlated with the severity of cerebral edema in patients with AICH in the basal ganglia (r=0.324, 0286, 0.305; p =0.021, 0.037, 0.029), whereas levels of IL-10 were negatively correlated with cerebral edema of these patients (r=-0.336, p =0.017).

Discussion

ICH can result in cerebral edema, increased intracranial pressure and other severe complications affecting the prognosis of the disease. Cerebral edema is the major cause of secondary cerebral injury after ICH and can further reduce blood supply to the brain, disrupt intracellular environment of neural cells and aggravate injury of neural cells. Hence, PHE becomes an important pathological factor causing death and disability after ICH[9,10]. The study showed that perihematomal lesions are observed in 60% of patients within 5 hours of ICH and these lesions are likely to be resulted from clot retraction of ICH[11]. Hydrostatic pressure and clot retraction are two major mechanisms underlying PHE. In addition, blood-brain barrier disruption caused by activated leukocytes and thrombin induces an inflammatory response, which is more severe than hemorrhagic damage[12]. Elevation in levels of inflammatory cytokines, including IL-4, IL-6, IL-8 and IL-10 as well as infiltration of neutrophils can occur at the early stage of ICH. Therefore, it is of great importance to investigate the expression of inflammatory cytokines and its relationship with cerebral edema in patients with acute basal ganglia hemorrhage.

IL-4 is involved in inflammation and immune responses, mainly by activating T cells and exerting immunomodulatory effects on B cells, T cells, master cells, macrophages and hematopoietic cells[13]. IL-4 can induce the secretion of both granulocytes and macrophages, enhance cell-mediated cytotoxicity as well as phagocytosis of neutrophils, and accelerate the migration of neutrophils to the site of the lesion[14,15]. The present study showed that serum levels of IL-4 peaked 1 day after admission and decreased subsequently in patients with acute basal ganglia hemorrhage, its level was positively correlated with the severity of cerebral edema. IL-6, an inflammatory factor produced by monocyte/macrophages, fibroblasts, B lymphocytes and T lymphocytes, can induce chemotaxis of monocytes-macrophages, induce the activation, proliferation and differentiation of T cells as well as the production and secretion of immunoglobulins, involving in inflammation and immune response[16,17]. The present study demonstrated that serum level of IL-6 peaked 1 day after admission and reduced thereafter, and its level was positively correlated with severity of cerebral edema in patients with acute basal ganglia hemorrhage. IL-8, an inflammatory cytokine produced and released from mononuclear cells, endothelial cells, macrophages and fibroblasts, plays a role in activating neutrophils by inducing morphological alteration of neutrophils and release of activated substances from these cells under ischemia and hypoxia, leading to regional inflammatory response. IL-8 is an important neutrophil chemotactic factor by promoting cell adhesion and aggregation, causing injury of endothelial cells and basement membrane of intracerebral capillaries and inducing vasogenic edema and neuronal injury[18,19]. This study found that serum levels of IL-8 peaked 1 day after admission and declined afterward. The IL-8 level was positively correlated with severity of cerebral edema in patients with acute basal ganglia hemorrhage. IL-10 is a potent anti-inflammatory factor, which can suppress multiple steps in the development of inflammation and inhibit transcription of IL-6 as well as production and activation of pro-inflammatory cytokines[20]. IL-10 exhibits neuroprotective function. While having anti-inflammatory properties, IL-10 can regulate the sensitivity of neurons to the toxicity of excitatory amino acids, exerting neuroprotective function[21,22]. The present study showed that serum levels of IL-10 peaked 3 days after admission and its level was negatively correlated with the severity of the cerebral edema in patients with acute basal ganglia hemorrhage.

Conclusions

Serum levels of IL-4, IL-6, IL-8 and IL-10 are significantly elevated in patients with acute basal ganglia hemorrhage. Levels of IL-4, IL-6 and IL-8 are positively correlated with severity of cerebral edema. However, the IL-10 level is negatively correlated with the severity of the cerebral edema. Hence, the inflammatory response is closely associated with the cerebral edema.

Conflicts of interest

The authors declare no conflicts of interest.

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