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The Expression Levels of Serum IL-1β, TNF-α and IL-6 in Patients with Acute Cerebral Infarction and Their Correlation with the Severity of Cerebral Edema

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Keywords

Acute cerebral infarction, Interleukin-1β, Tumor necrosis factor-a, Interleukin-6

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Abstract

Objective To analyze the expression levels of serum IL-1β, TNF-α and IL-6 in patients with acute cerebral infarction (ACI) and their correlation with the severity of brain edema. **Methods** A total of 90 ACI patients admitted to our hospital from January 2019 to January 2022 were selected as ACI group, and 60 healthy subjects were selected as healthy control group. The expression levels of interleukin-1 β (IL-1β), tumor necrosis factor-a (TNF-α) and interleukin-6 (IL-6), the disturbance coefficient of cerebral electrical impedance (CEI) on the affected side and the changes of serum factor levels in ACI patients with different degrees of disease were compared between the two groups. The correlation between serum factors and the severity of cerebral edema was analyzed by Pearson correlation method. **Results** The expression levels of IL-1β, TNF-α and IL-6, and CEI disturbance coefficient in the affected brain of the patients in ACI group were obviously higher than those in the healthy control group (P<0.05). The levels of plasma IL-1β, TNF-α, IL-6 and CEI disturbance coefficient in moderate and severe group were significantly higher than those in mild group (P<0.05). The plasma levels of AIM2, IL-1β and IL-18 in severe group were significantly higher than those in moderate group (P<0.05). In ACI group, the disturbance coefficient of CEI was positively correlated with the levels of serum IL-1β, TNF-α and IL-6 (P<0.05). **Conclusion** The expression levels of serum IL-1β, TNF-α and IL-6 in ACI patients are positively correlated with the severity of brain edema.

Introduction

When acute cerebral infarction (ACI) occurs, ischemia and hypoxia in brain tissues can activate the immune system to release a large number of inflammatory mediators, which can promote the activation of neutrophils in peripheral blood to infiltrate into cerebral ischemic tissues, secreting a variety of proteolylic enzymes and pro-inflammatory proteases to affect the venous return of surrounding brain tissues, thereby increasing the risk of localized cerebral edema [1-3]. In order to improve the symptoms of cerebral edema in patients with ACI, the key is to find the cause of cerebral edema in patients with ACI. Dongfang Xiao et al. showed that serum inflammatory factors may be related to neurological impairment severity, cerebral infarction volume and prognosis of the patients with ACI. At present, there are relatively few clinical studies on the use of serum inflammatory factors to evaluate cerebral edema in patients with ACI. Therefore, this study tested inflammatory factors such as Interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), and analyzed the correlation between serum factors and cerebral edema so as to provide an insight for the clinical treatment of this disease. The results were shown as follows.

Materials and methods

General data

A total of 90 ACI patients admitted to our hospital from January 2019 to January 2022 were selected as ACI group, and 60 healthy subjects were selected as healthy control group. At the same time, according to the National Institutes of Health Stroke Scale (NIHSS), the patients on admission were scored and divided into following groups based on the neurological impairment severity: mild group (n=36, NIHSS score ≤ 5 points), moderate group (n=33, 5 <NIHSS score ≤15) and severe group (n=21, NIHSS score >15). This study was approved by the ethics committee of our hospital, and all patients signed the written informed consent. The general data between the two groups were not significantly different and were comparable (P > 0.05), which was shown in Table 1.

Table 1 Comparison of the general data between the two groups

Group	Case	Sex (case)		Age
		male	female	
ACI group	90	46	44	62.45±10.49
Healthy control group	60	32	28	62.82±7.85
χ^2/t		0.071		-0.233
P		0.790		0.816

Inclusion criteria

① Patients were diagnosed following the diagnostic criteria for ACI in *Guidelines for the diagnosis and treatment of acute ischemic stroke in China 2018* [4]. Patients with clear consciousness; ② All patients were at the first onset and the onset time was less than 48 hours.

Exclusion criteria

① Patients combined with severe primary diseases of brain, liver and kidney or with mental illness; ② Patients were recently subjected to radiation therapy, chemotherapy, or immunosuppressive therapy; ③ Patients had other brain diseases except acute cerebral infarction.

Therapeutic methods

① Detection of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6): 5 ml of vein blood from each patient with an empty belly in the two groups was collected on admission into a vacuum blood collection tube containing anticoagulation, centrifuged to separate the plasma, and quickly stored in a -80°C low-temperature

refrigerator for testing. The levels of IL-1β, TNF-α, and IL-6 were measured by an enzyme-linked immunosorbent assay.

② The disturbance coefficient of cerebral electrical impedance (CEI) detection: The BORN-BE non-invasive cerebral edema dynamic monitor was used to monitor the CEI of the cerebral hemisphere on the affected side of patients with ACI. Continuous monitoring was performed twice in the patients with ACI, 25 min/time, and the average value of the cerebral edema indexes in each patient with ACI was calculated based on the two cerebral edema indexes obtained before, which was the result.

Statistical analysis

All data was processed using SPSS 20.0 software. Enumeration data were compared using χ^2-test. Measurement data are expressed as mean ± standard deviation ($\bar{x}\pm s$). Independent-sample *t*-test was used for the comparisons between two groups and one-way analysis of variance (ANOVA) for the comparisons between other multiple groups. The LSD test was used for pairwise comparison between groups, and the Pearson correlation method was used for correlation analysis. $P < 0.05$ was considered as a statistically significant difference.

Results

Comparison of IL-1β, TNF-α, and IL-6 expressions and CEI disturbance coefficient on the affected side between the two groups

The expression levels of IL-1β, TNF-α and IL-6 in ACI group and CEI disturbance coefficient in the affected brain were significantly higher than those in the healthy control group, as shown in Table 2.

Table 2 Comparison of IL-1β, TNF-α, and IL-6 expressions and CEI disturbance coefficient on the affected side between the two groups ($\bar{x}\pm s$)

Group	Case	IL-1β（pg/mL）	TNF-α（ng/mL）	IL-6（ng/mL）	Disturbance coefficient of CEI
ACI group	90	79.20±10.77	80.80±10.86	15.09±1.87	8.46±0.93
Healthy control group	60	35.02±8.56	9.75±2.09	3.01±0.25	6.58±0.59
t		26.647	50.010	49.688	13.897
P		0.000	0.000	0.000	0.000

Changes of serum factor levels in ACI patients with different degrees of disease

The levels of plasma IL-1β, TNF-α, IL-6 and CEI disturbance coefficient in moderate and severe group were significantly higher than those in mild group. The plasma levels of AIM2, IL-1β and IL-18 in severe group were significantly higher than those in moderate group, which was displayed in Table 3.

Table 3 Changes of serum factor levels in ACI patients with different degrees of disease ($\bar{x}\pm s$)

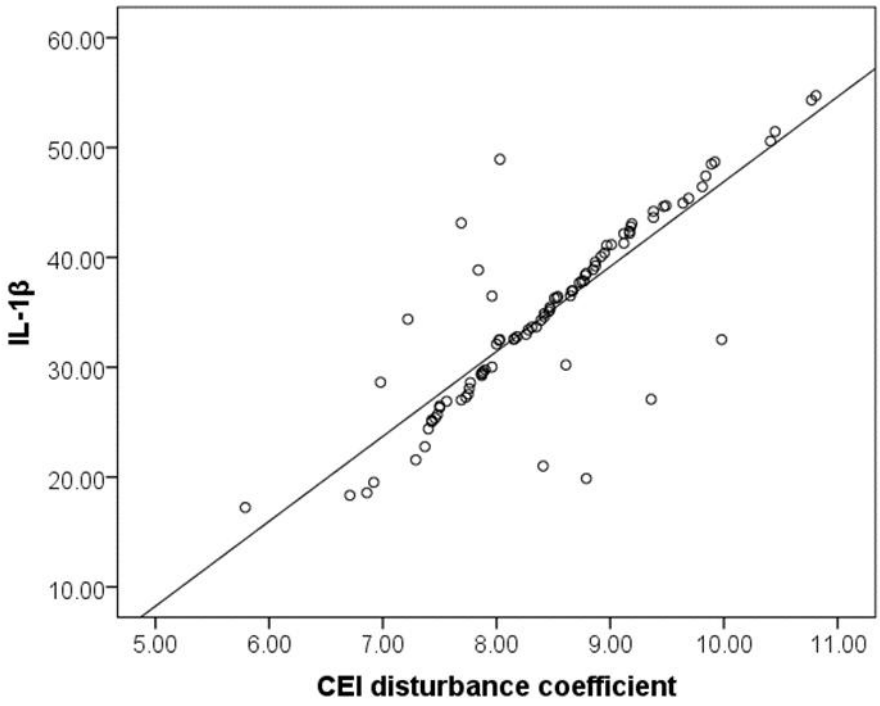
Group	Case	IL-1β（pg/mL）	TNF-α（ng/mL）	IL-6（ng/mL）	Disturbance coefficient of CEI
Mild group	36	28.66±6.51	77.25±7.37	13.59±1.13	7.58±0.48
Moderate group	33	35.71±4.79	81.28±8.02	15.41±1.26	8.63±0.25
Severe group	21	44.85±6.32	86.13±9.32	17.33±1.22	9.72±0.52
F		50.491	8.078	65.844	174.093
P		0.000	0.001	0.000	0.000

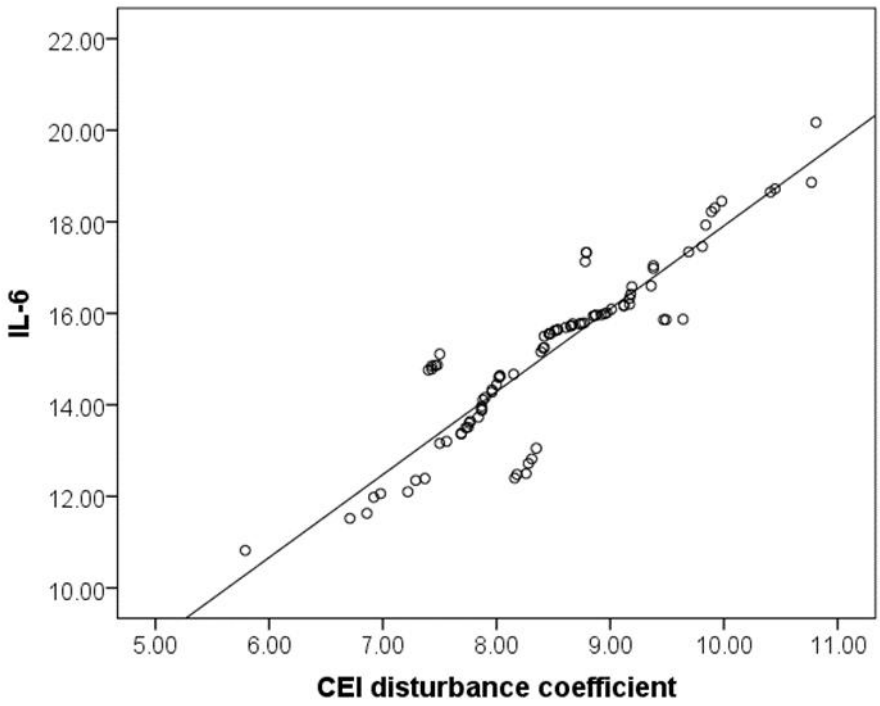
Correlation between serum factors and the severity of cerebral edema

In ACI group, the disturbance coefficient of CEI was positively correlated with the levels of serum IL-1β, TNF-α and IL-6, seen in Table 4.

Table 4 Correlation between serum factors and the severity of cerebral edema

Index		IL-1β	TNF-α	IL-6
Disturbance	*r*	0.844	0.415	0.899
coefficient of CEI	*P*	0.000	0.000	0.000





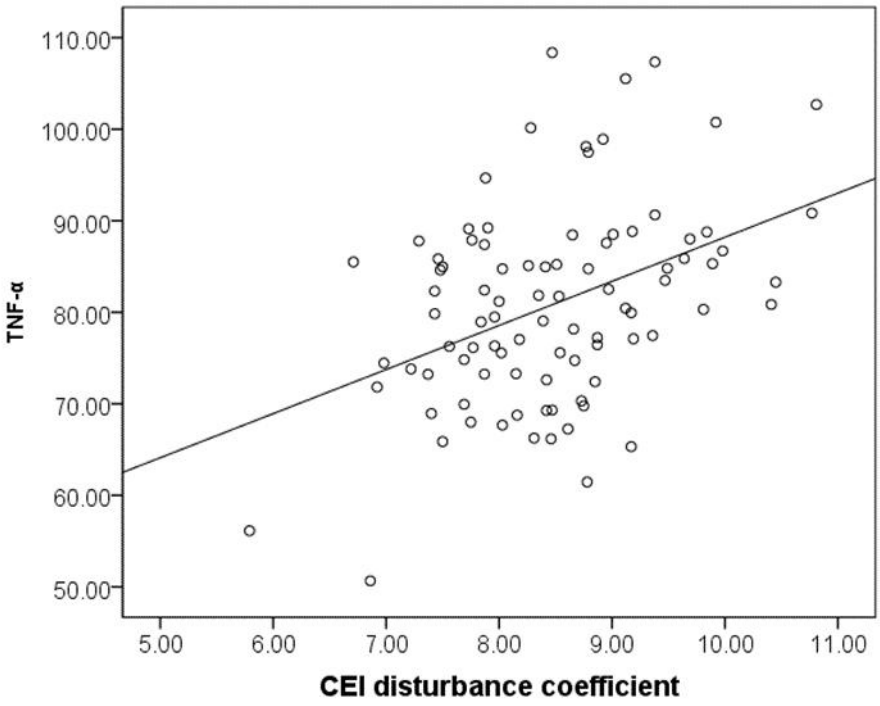


Figure 1 Correlation between serum factors and the severity of cerebral edema

Discussion

Long-term hypertension or hyperglycemia can cause the damage to the intima of vascular wall and the dysfunction of endothelial cell, resulting in continuous shrinkage of the lumen, slower blood flow, thrombogenesis in the body, thereby triggering blood blockage in the brain, which is the common pathogenic factors of ACI [5-6]. ACI has a high disability rate, accounting for 2/3 of all patients. It will bring serious consequences to individuals, families and society, so we should attach great attention to it. However, there is still no better treatment for ACI [7]. According to the previous study, inflammatory factors are closely related to the degree of cerebral edema in patients with ACI [8]. Therefore, in this study, we tested the levels of IL-1β, TNF-α, and IL-6 in the patients with ACI, and analyzed the correlation between serum factors and severity of brain edema, with the aim to provide an insight for the clinical treatment of this disease.

CEI monitoring technology refers to the one which applies an appropriate current to the human body through electrodes attached to the surface of the human body, monitoring the potential change of the specific boundaries in the brain through electrical bioimpedance measurement technology, thereby calculating the index reflecting the edema; the higher the CEI disturbance coefficient on the affected side is, the worse the brain edema condition is [9]. The results of this study showed that the expression levels of IL-1β, TNF-α and IL-6 and CEI disturbance coefficient in the affected brain of the patients in ACI group were significantly higher than those in the healthy control group. The levels of plasma IL-1β, TNF-α, IL-6 and CEI disturbance coefficient of the patients in moderate and severe group were significantly higher than those in mild group. The plasma levels of AIM2, IL-1β and IL-18 of the patients in severe group were significantly higher than those in moderate group. The above results confirmed that the expression levels of IL-1β, TNF-α, IL-6 and CEI disturbance coefficient in the affected brain can reflect the severity of patients with ACI. After cerebral infarction, the antigen stimulates the immune system, causing a strong immune response in the body and the further activation of monocytes-macrophages to release a large amount of IL-1β, TNF-α, and IL-6, which aggravates the body's inflammatory response

[10]. IL-1β is mainly secreted by macrophages, which is an important mediator of inflammatory response. The level of IL-1β mRNA is significantly increased in the patients with ACI, which promotes the production of abundant vascular cell adhesion molecule (VCAM). After VCAM binds to ligands, neutrophils adhere to blood vessels and harmful inflammatory mediators are continuously released, causing a large number of inflammatory substances to accumulate in brain parenchyma, thereby triggering an inflammatory response in brain tissues and the necrosis of brain tissues. TNF-α enhances the neurotoxicity of glutamic acid by inhibiting glutamine synthetase activity in neuronal cells. When the concentration of glutamate is abnormal, N-methyl-D-aspartate receptor (NMDAR) will be activated, causing excessive calcium in cells and the activation of neutral proteinase-protein kinase, which blocks protein metabolism in cells and damages nerve cells, consequently further aggravating the brain tissue necrosis in the patients with ACI. When platelets or endothelial cells are activated by IL-6 mediation, the membranes of α granules and Weibel-Palade bodies rapidly fuse with the cell membrane, resulting in the rapid expression of P-selectin on the surface of cell, thereby mediating the activation of endothelial cells and neutrophils as well as the adhesion of platelets and endothelial cells, even directly mediating structural changes in brain microvessels. In addition, IL-6 also has chemotactic effects on mononuclear macrophages, which can promote the increase of mononuclear macrophages in the ischemic area around the cerebral hematoma, and promoting free radicals to induce lipid peroxidation, thereby further damaging neurons [10-11].

The present study showed that in ACI group, CEI disturbance coefficient was positively correlated with the levels of serum IL-1β, TNF-α and IL-6, which verified that the expression levels of serum IL-1β, TNF-α and IL-6 in ACI patients are positively correlated with the severity of brain edema. IL-1β can produce TXA2 by activating endothelial cells, which has a strong effect of constricting blood vessels, causing spasm or paralysis of cerebral blood vessels, dysfunction of microcirculation, and increased venous pressure, thereby resulting in cerebral metabolic disorders and cerebral edema. In addition, IL-1β reduces cAMP in platelets and increases free Ca^{2+}. After entering cells, extracellular $Ca2^{+}$ was overloaded in nerve cells, which activates ATP enzyme to increase ATP, damages the cytoskeleton system, affects the expression and regulation of fast-response genes in nerve cells, and even changes the brain capillary permeability, thereby aggravating the cerebral oedema [12]. TNFα and IL-6 are released through excitatory amino acids (EAA), opening the cation channel of the membrane, which promotes the influx of Na^{+}, the depolarization of the membrane, and the influx of Cl^{-} that can combine with Na^{+} to form sodium chloride, eventually increasing the intracellular osmotic pressure. In order to maintain the intracellular and extracellular osmotic pressure balance, water will enter the cells from the outside, forming intracellular edema. However, the production of intracellular acidic substances will increase the membrane permeability, which further aggravates the cell edema [13].

In conclusion, the expression levels of serum IL-1β, TNF-α and IL-6 in ACI patients are positively correlated with the severity of brain edema.

Acknowledgement

Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization, Y.N.C and C.C.Z; Data curation, J.H.G; Writing-Original draft, Y.N.C and H.X.L; Writing-review and editing, Y.X.L; All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Material

Not applicable.

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