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Changes of MCP−1, FKN, and related cytokines in the serum and cerebrospinal fluid in children with epidemic encephalitis B

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ABSTRACT

Objective: To explore the changes of MCP-1, FKN, and related cytokines in the serum and cerebrospinal fluid (CSF) in children with epidemic encephalitis B. **Methods:** A total of 40 children with epidemic encephalitis B who were admitted in our hospital from June, 2014 to June, 2017 were included in the study and divided into the severe group (n=15) and general group (n=25) according to the severity group. Moreover, 20 children who were suffered from oblique inguinal hernia, perineal adhesion, and cryptorchidism were served as the control group. The serum and CSF specimens were collected 24 h after admission and during the recovery period in children with epidemic encephalitis B. The serum specimen was collected 24 h after admission in the control group, and CSF specimen was collected during the lumbar puncture. ELISA was used to detect CMP-1, FKN, IL-1 β , IL-18, and TNF- α levels in the serum and CSF. CMP-1, FKN, IL-1 β , IL-18, and TNF- α levels in children with epidemic encephalitis B on the day after admission and 2-3 weeks after admission and in the control group were compared. The changes of CMP-1, FKN, IL-1 β , IL-18, and TNF- α in children with severe and general epidemic encephalitis B were observed. **Results:** CMP-1 and FKN levels in the serum and CSF in children with epidemic encephalitis B in the critical stage were significantly higher than those in the recovery stage and in the control group. The serum CMP-1 and FKN levels in children with epidemic encephalitis B during the recovery stage were not significantly different from those in the control group, while CMP-1 and FKN levels in CSF were significantly higher than those in the control group. CMP-1 and FKN levels in the serum and CSF in children with severe epidemic encephalitis B were significantly higher than those in the general group. IL-1 β , TNF- α , and IL-18 levels in the serum and CSF in children with epidemic encephalitis B during the critical stage were significantly higher than those during the recovery stage and in the control group. IL-1 β , TNF- α , and IL-18 levels in the serum and CSF in children with epidemic encephalitis B during the recovery stage were significantly higher than those in the control group. IL-1 β , TNF- α , and IL-18 levels in the serum and CSF in children with severe epidemic encephalitis B were significantly higher than those in the general group. **Conclusions:** CMP-1, FKN, IL-1 β , TNF- α , and IL-18 levels in the serum and CSF in children with epidemic encephalitis B are correlated with the severity degree, detection of which can contribute to estimate the clinical typing and condition change of epidemic encephalitis.

1. Introduction

Some researches demonstrate that epidemic encephalitis B is associated with the inflammatory reaction of nervous tissues caused by direct invasion of JEV, whose antigen induced immunoreaction plays an important role in the pathogenesis of epidemic encephalitis B, and the intensity degree is closely correlated with the condition and prognosis[1]. MCP-1 and FKN are mainly involved in regulating the migration of leukocytes, attracting inflammatory cells to aggregate in the inflammatory sites, repairing the tissues, and eliminating the necrotic tissues. It is testified that the abnormal expressions of CMP-1 and FKN exist in the serum and CSF in patients with various central nervous system diseases, which is associated with the severity degree[2]. The study is aimed to explore the clinical significance of CMP-1, FKN, IL-1 β , IL-18, and TNF- α in the serum and CSF in children with epidemic encephalitis B, and their correlation with the severity degree.

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2. Materials and methods

2.1. General materials

A total of 40 children with epidemic encephalitis B who were admitted in our hospital from June, 2014 to June, 2017 were included in the study, among which 26 were male, and 14 were female; aged from 2 to 11 years old, with an average of (5.9±1.2) years old. Inclusion criteria: (1) those who were in accordance with related diagnostic criteria of epidemic encephalitis B in Epidemiology[3]; (2) those whose JEV specific IgM antibody was positive. Those whose medical materials were not complete were excluded from the study. The patients were divided into the severe group (n=15) and the general group (n=25) according to the severity degree. Moreover, 20 children who were suffered from oblique inguinal hernia, perineal adhesion, and cryptorchidism were served as the control group, among which 12 were male, and 8 were female; aged from 2 to 10 years old, with an average age of (5.7±1.3) years old. All the parents had signed the informed consents. The comparison of age and gender between the two groups was not statistically significant (P>0.05).

2.2. Methods

The serum and CSF specimens were collected 24 h after admission and during the recovery period in children with epidemic encephalitis B. The serum specimen was collected 24 h after admission in the control group, and CSF specimen was collected during the lumbar puncture. The specimens were preserved at -80 ℃ in the refrigerator for detection. ELISA was used to detect CMP-1, FKN, IL-1 β , IL-18, and TNF- α levels in the serum and CSF. The kits were provided by Wuhan USCN Business Co. Ltd and Shanghai Jingmei Company. The operations were performed by the professionals according to the instructions.

2.3. Observation indicators

CMP-1, FKN, IL-1 β , IL-18, and TNF- α levels in children with epidemic encephalitis B on the day after admission and 2-3 weeks after admission and in the control group were compared. The changes of CMP-1, FKN, IL-1 β , IL-18, and TNF- α in children with severe and general epidemic encephalitis B were observed.

2.4. Statistical analysis

SPSS 19.0 software was used for the statistical analysis. The measurement data were expressed as mean ± SD, and t test was used. Chi-square test was used for the enumeration data. P<0.05 was regarded as statistically significant.

3.Results

3.1. Comparison of CMP–1 and FKN levels in the serum and CSF in epidemic encephalitis B in the critical stage and recovery stage and in the control group

CMP-1 and FKN levels in the serum and CSF in children with epidemic encephalitis B in the critical stage were significantly higher than those in the recovery stage and in the control group (P<0.05). The serum CMP-1 and FKN levels in children with epidemic encephalitis B during the recovery stage were not significantly different from those in the control group (P>0.05), while CMP-1 and FKN levels in CSF were significantly higher than those in the control group (P<0.05) (Table 1).

3.2. Comparison of CMP–1 and FKN levels in the serum and CSF between the severe group and the general group

CMP-1 and FKN levels in the serum and CSF in children with severe epidemic encephalitis B were significantly higher than those in the general group (P<0.05) (Table 2).

Table 1.

Comparison of CMP-1 and FKN levels in the serum and CSF in epidemic encephalitis B in the critical stage and recovery stage and in the control group.

Groups	n	CMP-1		FKN	
		Serum	CSF	Serum	CSF
Critical stage	40	514.64±307.45	435.48±276.17	7.65±4.87	3.92±2.45
Recovery stage	40	192.65±78.36*	125.72±28.75*	1.81±1.12*	0.67±0.15*
Control group	20	176.48±74.43*	93.18±18.34*#	1.69±0.92*	0*#

*P<0.05, when compared with the critical stage, #P<0.05, when compared with the recovery stage.

Table 2.

Comparison of CMP-1 and FKN levels in the serum and CSF between the severe group and the general group.

Groups	n	CMP-1		FKN	
		Serum	CSF	Serum	CSF
Severe group	15	897.32±135.67*	875.37±121.54*	11.75±3.21*	9.85±1.24*
General group	25	358.38±107.84	321.61±114.07	3.62±1.13	3.37±1.87

*P<0.05, when compared with the general group.

Table 3.

Comparison of IL-1 β , TNF- α , and IL-18 levels in the serum and CSF in epidemic encephalitis B in the critical stage and recovery stage and in the control group.

Groups	*n*	IL-1 β (μg/L)		TNF- α (ng/L)		IL-18 (pg/L)	
		Serum	CSF	Serum	CSF	Serum	CSF
Critical stage	40	0.81±0.15	0.74±0.12	93.61±25.45	129.57±38.74	93.57±16.71	158.36±21.36
Recovery stage	40	0.48±0.09*	0.43±0.08*	8.87±2.56*	9.46±3.75*	65.43±8.29*	56.42±15.39*
Control group	20	0.23±0.06*#	0.25+0.12*#	2.35±1.28*#	3.75±1.22*#	52.36±14.17*#	35.74±9.85*#

*P<0.05, when compared with the critical stage, #P<0.05, when compared with the recovery stage.

Table 4.

Comparison of IL-1 β , TNF- α , and IL-18 levels in the serum and CSF between the severe group and the general group.

Groups	*n*	IL-1 β (μg/L)		TNF- α (ng/L)		IL-18 (pg/L)	
		Serum	CSF	Serum	CSF	Serum	CSF
Severe group	15	0.95±0.13*	0.98±0.15*	169.45±17.24*	176.49±17.93*	175.46±29.86*	217.63±26.84*
General group	25	0.62±0.14	0.69±0.16	79.42±15.66	95.77±14.52	97.42±23.58	107.41±21.49

*P<0.05, when compared with the general group.

3.3. Comparison of IL–1 β , TNF– α , and IL–18 levels in the serum and CSF in epidemic encephalitis B in the critical stage and recovery stage and in the control group

IL-1 β , TNF- α , and IL-18 levels in the serum and CSF in children with epidemic encephalitis B during the critical stage were significantly higher than those during the recovery stage and in the control group (P<0.05). IL-1 β , TNF- α , and IL-18 levels in the serum and CSF in children with epidemic encephalitis B during the recovery stage were significantly higher than those in the control group (P<0.05) (Table 3).

3.4. Comparison of IL–1 β , TNF– α , and IL–18 levels in the serum and CSF between the severe group and the general group

IL-1 β , TNF- α , and IL-18 levels in the serum and CSF in children with severe epidemic encephalitis B were significantly higher than those in the general group (P<0.05) (Table 4).

4. Discussion

Epidemic encephalitis B is an acute infectious disease of central nervous system caused by JEV, with main pathological changes of neuron degeneration and necrosis, microglial cell proliferation, and softening focus formation caused by brain parenchyma inflammation. Under the role of JEV, obvious apoptosis can occur in vascular endothelial cells in the brain, resulting in increased vascular wall permeability; therefore, JEV can successfully pass through the blood brain barrier to enter the brain tissues. Some scholars also argue that the alteration of blood brain barrier permeability occurs after JEV infection which can induce the expressions of chemotactic factors and inflammatory cytokines, inhibit the synthesis of tight junction TJ protein between the vascular endothelial cells, and increase the blood brain barrier permeability, thus damaging the brain neurons[4,5].

Chemotactic factors are a kind of cytokines with chemotaxis which can promote the migration of inflammatory cells to the inflammtory damage sites, while MCP-1 and FKN belong to different subfamily members of chemotactic factors. MCP-1 can promote and activate the monocytes, dendritic cells, basophilic granulocytes, and T lymphocytes, and must combine with GPCRs to initiate the sequential inflammatory reaction[6]. The peripheral blood MCP-1 is mainly secreted by the vascular endothelial cells and monocytes. It is verified that JEV initially breeds in the monocyte-phagocyte system, and then enter the blood circulation. MCP-1 of central nervous system is mainly secreted by the microglial cells and neurons. After entering the brain parenchyma, JEV can affect the microglial cells, damaging the neurons; therefore, the elevation of MCP-1 level in CSF may be associated with the neuron damage[7]. FKN is the only member of CX3C subfamily, and can be divided into the membrane-associated type and soluble type, among which the membrane-associated type FKN can induce the activation of vascular endothelial cells, promote the adhesion of activated endothelial cells and inflammatory cells, and provide a premise for the migration and aggregation of inflammatory cells to the damaged sites, while the soluble FKN has a chemotaxis on the monocytes and T lymphocytes, and can facilitate their aggregation in the damaged sites to be involved in the inflammatory reaction[8]. The peripheral blood FKN can be produced by the dendritic cells and vascular endothelial cells, whose secretion is significantly increased after the stimulation of inflammatory mediators. FKN of the central nervous system is mainly produced by the neurons, exists in a membrane-associated type in a normal physiological state, which can be turned into the soluble type under the effect of protease after neuron stimulation, which can promote the aggregation of inflammatory cells in the damaged sites, and be involved in the inflammatory reaction[9]. The results in the study showed that CMP-1 and FKN levels in the serum

and CSF in children with epidemic encephalitis B in the critical stage were significantly higher than those in the recovery stage and in the control group (P<0.05); the serum CMP-1 and FKN levels in children with epidemic encephalitis B during the recovery stage were not significantly different from those in the control group (P>0.05), while CMP-1 and FKN levels in CSF were significantly higher than those in the control group (P<0.05), indicating that CMP-1 and FKN are involved in the pathogenesis of epidemic encephalitis B, whose increased expressions suggest the brain parenchyma damage. In the study, FKN was not detected in CSF in the control group, which may be explained by the fact that FKN exists in neurons in a membrane-associated type, while FKN in CSF in children with epidemic encephalitis B is mainly of the soluble type. The results in the study showed that CMP-1 and FKN levels in the serum and CSF in children with severe epidemic encephalitis B were significantly higher than those in the general group (P<0.05), indicating that the elevation degree of CMP-1 and FKN is positively correlated with the brain parenchyma damage degree.

Some researches demonstrate that[10] the immunological mechanism in patients with epidemic encephalitis B plays an important role in the cerebral injury. IL-1β, TNF-α, and IL-18 are the cytokines with various functions, and play a leading role in the cerebral damage in patients with epidemic encephalitis B. IL-1β is closely associated with the central system disease. When there is a hypoxic-ischemic brain damage, the neuroglial cells are destroyed, IL-1β release is increased, which can cause the excessive inflammatory reaction and reperfusion damage of brain tissues through various immunological mechanisms, and promote the progression of brain damage[11]. IL-18 is a kind of multi-effect cytokine, and can induce T cell and NK cell to produce IFN-γ. In the brain tissues, IL-18 can induce the production of chemotactic factors and adhesion factors, and is involved in the destruction of brain tissues after ischemia and hypoxia. IL-18 can also stimulate the production of IL-1β and TNF-α, and promote the excessive inflammatory reaction of brain tissues[12]. TNF-α as the pro-inflammatory cytokine, can promote the synthesis of chemotactic factors and excessive inflammatory reaction, activate PLA2, cause the hydrolysis of nerve cell membrane phospholipid, induce the cell apoptosis, and destroy the blood brain barrier[13]. The results in the study showed that IL-1β, TNF-α, and IL-18 levels in the serum and CSF in children with epidemic encephalitis B during the critical stage were significantly higher than those during the recovery stage and in the control group (P<0.05); IL-1β, TNF-α, and IL-18 levels in the serum and CSF in children with epidemic encephalitis B during the recovery stage were significantly higher than those in the control group (P<0.05); IL-1β, TNF-α, and IL-18 levels in the serum and CSF in children with severe epidemic encephalitis B were significantly higher than those in the general group (P<0.05), indicating that IL-1β, TNF-α, and IL-18 can mediate the cerebral injury through various immunological mechanisms, and are involved in the inflammatory reaction of brain tissues, whose levels are consistent with the clinical typing of epidemic encephalitis B; therefore, clinical detection of the changes of IL-1β, TNF-α, and IL-18 in the serum and CSF can be served as a reference evidence for the clinical typing of epidemic encephalitis B.

In conclusion, CMP-1, FKN, IL-1β, TNF-α, and IL-18 levels in the serum and CSF in children with epidemic encephalitis B are correlated with the severity degree, detection of which can contribute to estimate the clinical typing and condition change of epidemic encephalitis.

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