CHANGES IN IFN-Γ AND IL-4 LEVELS IN THE SERUM AND CSF OF PATIENTS WITH SUPPURATIVE MENINGITIS AND VIRAL ENCEPHALITIS

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ABSTRACT

Objective*: By detecting and comparing IFN – γ and IL-4, and their dynamic changes in the CSF and serum of children with central nervous system infections, we explored the values of IFN-γ and IL-4 levels in the differential diagnoses of suppurative meningitis and viral encephalitis.*

Methods: *From January to December 2019, 80 children with central nervous system infections were admitted to our hospital; 40 children had suppurative meningitis (suppurative group) and 40 had viral encephalitis (viral group). In addition, 40 children who visited our hospital for health examinations in the same period were included as the control group. The IFN - γ and IL-4 levels in the serum and CSF of the three groups were detected in the acute stage and in the recovery stage, respectively.*

Results: *In the acute stage, levels of IFN - γ and IL-4 in the serum and CSF of the suppurative and viral groups were higher than they were in the control group (P<0.05); while the IFN - γ in the viral group was higher than it was in the suppurative group, IL-4 was lower than it was in the suppurative group (P<0.05). In the recovery stage, the levels of IFN - γ and IL-4 in the serum and CSF in the suppurative and viral groups were higher than they were in the control group (P<0.05), while there was no difference between the suppurative and viral groups (P>0.05). A within-group comparison revealed that the levels of IFN-γ and IL-4 in the serum and CSF of the acute-stage suppurative and viral groups were higher than they were in the recovery period of the corresponding groups (P<0.05). There was a significant difference in the levels of IFN - γ and IL-4 among the three groups (P<0.05).*

Conclusion: *IFN- γ and IL-4 may be involved in damage to the function of the blood-CSF barrier in patients with central nervous system infections. Detecting the levels of IFN- γ and IL-4 in the serum and CSF of patients with central nervous system infections in the acute phase can help to distinguish acute purulent meningitis and viral encephalitis.*

Keywords: *Purulent meningitis, viral encephalitis, serum, CSF, interferon gamma, interleukin-4.*

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Introduction

Intracranial infection is one of the most common infectious diseases of the nervous system in childhood, and includes suppurative and viral infections[1]. At present, it is generally believed that, after the virus invades the central nervous system and causes damage to brain tissue, it can gradually activate the body's autoimmune system. In the early stage of infection, the symptoms of toxic encephalitis and suppurative meningitis are similar, and the clinical manifestations are not typical. As the examination of CSF may not reveal characteristic changes, it is not easy to make a diagnosis or differential diagnoses[2, 3]. Therefore, the detection of central nervous system injury markers has gradually become one of the hot topics in medical research. In this paper, IFN - γ, IL-4, and their dynamic changes in the CSF and serum of children with central nervous system infections, were detected and compared to explore the values of IFN - γ, IL-4 levels in the differential diagnoses of suppurative meningitis and viral encephalitis. The following sections provide a detailed report of this study.

Data and methods

General information

From January to December 2019, 80 children with central nervous system infections were admitted to our hospital; 40 children has suppurative meningitis (suppurative group) and 40 had viral encephalitis (viral group). In addition, 40 children who visited our hospital for health examinations in the same period were included as the control group. There were 28 boys and 12 girls in the suppurative group, with an average age of 7.4±1.8 years. The viral group included 26 boys and 14 girls with an average age of 8.2±2.1 years, while there were 25 boys and 15 girls in the control group (0.8-15 years), with an average age of 7.9±2.2 years. A comparison of the ages and genders in the three groups is provided in Table 1.

Group	Number of Cases	Gender (*n*)		Age (years)	
		Male	Female	Age range	Average age
Suppurative group	40	28	12	0.5-12	7.4±1.8
Viral group	40	26	14	0.8-14	8.2±2.1
Control group	40	25	15	0.8-15	7.9±2.2
F value		1.263		0.834	
P value		0.093		0.137	

Table 1: Age and gender comparisons for the three groups.

Inclusion and exclusion criteria

The subjects were selected for this study based on the following criteria:

• Children in the suppurative and viral groups were diagnosed based on history, etiology, and imaging examinations;

• Children in the control group were excluded from having central nervous system infections;

• The total course of disease in all the children was not longer than three days; and

• Children in the control group should have indications of lumbar puncture due to other brain diseases.

The exclusion criteria were as follows:

• Patients with other serious nervous system and mental diseases;

• Patients with immune deficiency diseases;

• Patients with other infectious intracranial diseases and other complications; and

• Patients with congenital brain malformation, or brain trauma and brain tumors.

Method

CFS and serum samples were collected from the suppurative meningitis group, the viral encephalitis group, and the control group on the same day of the acute phase within three days of onset (within 24 hours following admission) and in the recovery phase (within two to three weeks following clinical treatment). CSF was extracted via a lumbar puncture under aseptic conditions. After routine and cytological examinations of the CSF, another 1.5 mL of CSF was retained; at the same time, 2 mL of blood from the elbow vein was extracted and placed in an EP tube. After standing at room temperature for two hours, the heart was separated at 3000 rpm for 15 minutes, supernatant was collected and placed separately into the EP tube; the samples were numbered, allocated a collection date and time, and frozen at -20 °C for inspection. The concentrations of IFN - γ and IL-4 in CSF and serum were measured by ELISA, and the IFN - γ / IL-4 was calculated.

Statistical methods

SPSS22.0 statistical software was used for data processing and analysis, in which a t-test was used for data measurement conforming to normal distribution, a group t-test was used for comparisons among groups, and a mean ± standard deviation ($\bar{x}\pm s$) was used for expression; a χ^2 test was used to count the data. The test standard was set as $\alpha=0.05$, $P<0.05$, which considered that the difference was statistically significant.

Results

Comparison of the IFN-γ in the CSF and serum among the three groups during the acute and recovery phases

The statistics pertaining to IFN - γ in the CSF and serum in the acute and recovery phases of patients in the suppurative, viral, and control groups are presented in Table 2.

Group	Phase	Number of cases	IFN-γ (pg/mL)	
			CSF	Serum
Suppurative group	Acute phase	40	5.47±1.46*#	14.75±4.16*
	Recovery phase		3.19±0.59	12.25±1.69
Viral group	Acute phase	40	9.26±1.15*	28.96±3.87*
	Recovery phase		3.87±0.79	14.12±1.53
Control group		40	2.42±0.53	9.16±2.24

Table 2: Comparison of the IFN-γ in the CSF and serum among the three groups during the acute and recovery phases.

*Note: *indicates that there is statistical difference compared to the recovery period and control group (P<0.05); #indicates that there is statistical difference in IFN - γ in the CSF and serum in the acute phase of the suppurative group and the viral group (P<0.05).*

Comparison of IL-4 in the CSF and serum among the three groups of children in the acute phase and recovery phases

The statistics pertaining to the levels of IL-4 in the CSF and serum in the acute and recovery phases of children in the suppurative, viral, and control groups are presented in Table 3.

Group	Phase	Number of cases (*n*)	IL-4 (pg/mL)	
			CSF	Serum
Suppurative group	Acute phase	40	42.48±5.1*#	92.07±11.23*
	Recovery phase		14.52±2.14	46.24±4.75
Viral group	Acute phase	40	21.43±1.7*	53.21±8.16*
	Recovery phase		14.76±1.45	43.02±9.21
Control group		40	9.78±1.11	40.09±4.67

Table 3: Comparison of IL-4 in the CSF and serum among the three groups of children in the acute and recovery phases.
*Note: *indicates that there is statistical difference compared to the recovery period and control group (P<0.05); #indicates that there is statistical difference in IL-4 in the CSF and serum between the acute phase of the suppurative group and of the viral group (P<0.05).*

Comparison of the IFN - γ / IL-4 ratio in the CSF and serum of the three groups in the acute stage

The ratio of IFN-γ/IL-4 in the CSF and serum in the acute phase of the three groups of patients is shown in Table 4.

Group	Number of cases (*n*)	IFN-γ/IL-4	
		CSF	Serum
Viral group	40	0.512±0.045*#	0.498±0.116*#
Suppurative group	40	0.140±0.034*	0.153±0.039*
Control group	40	0.367±0.062	0.289±0.021

Table 4: Comparison of the IFN - γ/IL-4 ratio in the CSF and serum of the three groups in the acute phase.
*Note: *indicates a statistical difference compared to the control group, P<0.05; #indicates a statistical difference compared to the suppurative group, P<0.05.*

Discussion

Intracranial infection is one of the most common central system infections in children. Intracranial infection has multiple symptoms, poor prognosis, and has a high mortality rate.

Intracranial infection can be divided into the following types according to the location of the lesions involved:

• Meningitis: the infection site of meningitis is more limited, occurs in the pia mater, there is no damage to the brain parenchyma, and the clinical manifestations are mainly signs of meningeal stimulation[4-6].

• Encephalitis: the infection involves the brain parenchyma but, as the meninges involved are in a small range, the clinical symptoms are mainly damaged brain parenchyma, epilepsy, and poor location[7].

• Meningeal encephalitis: as meningeal encephalitis involves the brain tissue and meninges, the symptoms are more complex[8].

• Encephalomyelitis: a the name suggests, while encephalomyelitis involves the brain substance, it also invades the spinal cord to a certain extent.

Intracranial infections occur more easily in children. The reason is that normal adults have a blood-brain barrier; following infection, pathogenic microorganisms and products of decomposition cannot penetrate the barrier and damage the meninges and brain parenchyma.

However, the blood-brain barrier is not well developed in infants and children, and the permeability is significantly higher than it is in in adults, thus making it easier for pathogenic microorganisms and toxins to penetrate the blood-brain barrier. In addition, since the development of the body's immune system is not perfect and the regulatory function is low, immune disorders and inflammatory reactions can spread easily following an infection. Therefore, the incidence of central nervous system infection in infants and children is higher than it is in adults, and the prognosis is worse[9, 10].

When a pathogen enters the body, it can activate the immune system; once the immune system has been activated, it releases a large number of inflammatory factors to carry out immune response and immune regulation. Intracranial infections are no exception. Following the occurrence of intracranial infection, a considerable number of cytokines are also released. In a prospective observational study, Ye et al.[11] found that the combination of CSF IL-6 and CSF/blood IL-6 was a good biomarker for identifying bacterial meningitis, which could improve the efficiency of diagnosis. Dionne et al.[12] cultured slices of the brains of virus-infected mice, and found that the infected nerve cells released IL6, CXCL10, chemokines, and murine IL8.

These studies showed that a variety of cytokines are released to participate in the immune process following intracranial infection.

In our research, we chose to study IL-4 and IFN - γ. The results showed that, in the acute phase, IFN

- γ and IL-4 levels in the serum and CSF of the suppurative and viral groups were higher than they were in the control group (P<0.05); while the IFN - γ levels in the viral group were higher than they were the suppurative group, the level of IL4 was lower than it was in the suppurative group (P<0.05). In the recovery phase, the levels of IFN - γ and IL-4 in the serum and CSF of the suppurative and viral groups were higher than they were in the control group (P<0.05), and there was no difference between the suppurative and the viral groups (P>0.05).

A within-group comparison showed that the levels of IFN - γ and IL-4 in the serum and CSF of the suppurative and viral groups in the acute phase were higher than they were in the recovery phase of the corresponding groups (P<0.05).

There was a significant difference in IFN - γ/IL-4 among the three groups (P<0.05). The symptoms of suppurative meningitis and viral encephalitis are not typical. Epidemiological studies have found that more than half of viral encephalitis cases lack pathogenic evidence[13].

The main biological functions of IFN - γ are to:

• Enhance the expression of MHC;

• Enhance the antigen presentation of T cells, and promote the proliferation and differentiation of T cells;

• Activate the innate immune cells, improve the ability of these cells to remove viruses, and secrete a variety of proinflammatory factors, which not only mediate the inflammatory reaction to eliminate the dissident, but also mediate the damage of inflammation to the body itself;

• Induce the infected cells to synthesize specific factors, and inhibit the replication, assembly, and release of viruses; and

• Participate in the cells' immune regulation.

Therefore, the level of IFN - γ is higher in patients with viral encephalitis than it is in patients with purulent meningitis (14). However, IL-4 is mainly secreted by Th2 cells, and its effect on humoral immunity is mainly manifested in enhancing the antigen-presenting ability of B lymphocytes, acting on different stages of B cell proliferation and differentiation, and inducing plasma cells to produce humoral immunity; thus, levels of IL-4 are higher in patients with suppurative meningitis[15].

In summary, IFN - γ and IL-4 may be involved in functional damage of the blood-CSF barrier in patients with central nervous system infections. The detection of IFN - γ and IL-4 in the serum and CSF of patients with central nervous system infections in the acute stage can help to distinguish suppurative meningitis and viral encephalitis in this stage.

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