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# A study on correlations of procalcitonin and interleukin-6 with viral meningitis

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**Abstract. – OBJECTIVE: To study the change rules of inflammatory factors in cerebrospinal fluid (CSF) and serum of patients with viral meningitis.**

**PATIENTS AND METHODS: 742 patients with suspected viral meningitis admitted to Department of Neurosurgery in our hospital from August 2012 to May 2016 were selected as research objects and retrospectively analyzed. 536 patients were diagnosed with viral meningitis by CSF with the lumbar puncture and brain computed tomography (CT), while the other 206 patients were diagnosed with non-infectious nervous system disease, as the control group. The levels of inflammatory factors interleukin-6 (IL-6) in peripheral blood and procalcitonin (PCT) in cerebrospinal fluid were detected and compared between two groups of patients.**

**RESULTS: Compared with those in control group, the white blood cell (WBC) count, and levels of serum IL-6 and PCT in cerebrospinal fluid of patients with viral meningitis were all increased ($p$<0.01). PCT and IL-6 were positively correlated with viral meningitis ($r$=0.8267, 0.9234). The sensitivity of the two items was 77.81% and 81.32%, respectively, and the specificity was 90.53% and 88.64%, respectively.**

**CONCLUSIONS: The levels of inflammatory factors IL-6 and PCT in serum and CSF of patients with viral meningitis are slightly increased. The detection of the expression levels of IL-6 and PCT in patients with viral meningitis is of great significance for the preliminary diagnosis and rehabilitation of viral meningitis.**

Key Words

PCT, IL-6, Viral meningitis, WBC count, Neutrophil count.

## Introduction

The diffuse inflammatory changes caused by attacks of viruses, bacteria, fungi, protozoa and other virulence factors against *pia mater* or spinal membrane are called meningitis[1]. Meningitis is a more serious disease that frequently occurs in children and needs to be treated within 12 hours after the onset. If not treated in time, it would cause permanent brain damage and even brain death[2]. Meningitis is generally divided into purulent meningitis (meningitis caused by pyogenic bacteria), tuberculous meningitis (meningeal non-suppurative inflammation caused by *Mycobacterium tuberculosis*), cryptococcal meningitis (fungus-caused meningitis), and viral meningitis (virus-induced central nervous system infection)[3]. Among them, viral meningitis is the most common kind of aseptic meningitis, with a course of more than 2 weeks, which has a certain self-limitation, with little difficulty in treatment and better prognosis effect[4]. Procalcitonin (PCT) is a hormone-free glycoprotein with extremely high sensitivity to viral infection and bacterial infection[5]. Interleukin-6 (IL-6) is an important factor that can stimulate the proliferation and differentiation of immune cells and enhance the metabolic capacity of the immune system in acute infection of the body[6]. According to Konstantinidis et al[7], PCT combined with C-reactive protein has a certain value in the early diagnosis of tuberculous meningitis, but the correlation between PCT and viral meningitis has not been analyzed in detail. This study aims to investigate the correlations of PCT and IL-6, two highly-sensitive markers of infectious diseases, with viral meningitis. It is possible to provide reference and guidance for future clinical diagnosis and treatment of viral meningitis.

## Patients and Methods

### General Data

742 patients with suspected viral meningitis were admitted to Department of Neurosurgery in the Affiliated Jiangyin Hospital of Southeast University of Medical College from August 2012 to May 2016. They were selected as research objects and retrospectively analyzed. Meningitis was diagnosed according to 2011 meningitis diagnosis guidelines[8], the number of cells increased up to 10-



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$500\times10^6$/L. Polymorphonuclear cells were dominant at early stages and lymphocytes were dominant 8 to 48 hours after. Protein levels can be mildly elevated, but sugar levels are normal. The virus can be isolated from throat swabs and stools in case of acute enterovirus infections. A total of 536 cases of viral meningitis were diagnosed by lumbar puncture cerebrospinal fluid routine test, biochemical and bacteriological examination and brain CT examination. 536 patients were diagnosed with viral meningitis by cerebrospinal fluid (CSF) with the lumbar puncture and brain computed tomography (CT), including 297 males and 239 females aged (8.54±6.63) years old. The other 206 patients were diagnosed with non-infectious nervous system diseases. These patients, including 157 males and 82 females aged (8.12±7.17) years old, were selected as the control group. The study was approved by the Ethics Committee of the Affiliated Jiangyin Hospital of Southeast University of Medical College.

### Inclusion and Exclusion Criteria

Inclusion criteria: patients with damaged brain parenchyma clinically caused by viruses; patients without space-occupying lesions detected by brain CT and magnetic resonance imaging (MRI); patients who were sent to the hospital within 10 hours after the onset of disease; patients with complete medical records. Exclusion criteria: patients who had received antibiotics or other drugs before admission; neonatal or lactating patients; patients with other cardiovascular or cerebrovascular diseases; patients who were bedridden for a long time. All of the above patients' guardians had signed the informed consent.

### Grouping and Methods

536 patients with viral meningitis were selected as the observation group, and the other 206 patients were as the control group. 4 ml cerebrospinal fluid of patients in each group were collected by lumbar puncture and divided into two parts (2 ml each). A part was used to detect the IL-6 and other inflammatory factors (CSF) by double antibody sandwich enzyme-linked immunosorbent assay (ELISA) using ELISA kit provided by Siemens (Berlin and Munich, Germany). The other part was centrifuged (4000 g/5 min); cerebrospinal fluid enolase (NES) was detected using NES-ELISA kit (Siemens, Munich, Germany). Moreover, 4 mL of venous blood were extracted from patients and centrifuged by a centrifugal machine (3000 dpm/s) for 5 min after standing at room temperature for 10 min, then the upper serum was taken and the serum PCT in patients was detected by immunoassay instrument (Roche, Basel, Switzerland). The correlations were analyzed.

### Statistical Analysis

The data were processed by Statistical Product and Service Solutions (SPSS Inc., Chicago, IL, USA) 22.0 software. Enumeration data were expressed by rate and $\chi^2$-test was used for intergroup comparison. Measurement data were expressed by ($\bar{x} \pm s$) and $t$-test was used for intergroup comparison. $p<0.05$ suggested that the difference was statistically significant.

## Results

### Clinical Data of Patients

According to the clinical data of patients, the gender, age, hospital delivery time (less than 10 hours), nationality, place of residence, family history, and whether the patient was an only child had no effects on the findings ($p>0.05$) (Table I).

### PCT and Cerebrospinal Fluid WBC, IL-6 Test Results

The level of PCT in the observation group was (0.82±0.34) μg/L, the cerebrospinal fluid WBC count was ($0.004\pm0.002\times10^9$), and the IL-6 was (7.26±1.54) pg/mg, which were all higher than those in the control group (0.25±0.21); the differences were statistically significant ($p<0.05$). Levels of sIL-6R, IL-1, IL-8, VEGF, and TNF-α in cerebrospinal fluid were also significantly higher than those in control group ($p<0.05$) (Table II).

### Correlation Analysis of PCT, IL-6 and Viral Meningitis

By correlation analysis, it could be seen that the levels of PCT and IL-6 were positively correlated with viral meningitis, and the correlation degrees were 0.8267 and 0.9234, respectively, which were the risk factors of viral meningitis (Figure 1).

### Receiver Operating Characteristic (ROC) Curve Analysis

By ROC curve analysis, it could be seen that the area under the curve of PCT was 0.806, and the 95% confidence interval (95% CI) of PCT was 0.701-0.921. The area under the curve of IL-6 was 0.866, and 95% CI of IL-6 was 0.752-0.956. The sensitivity of the two items was 77.81% and 81.32%, respectively, and the specificity was 90.53% and 88.64%, respectively (Table III, Figure 2).

**Table I.** Clinical data of patients [n(%)].

| | | Observation group n=536 | Control group n=239 | *p* |
|---|---|---|---|---|
| ***Gender*** | Male | 297 (55.41) | 157 (65.69) | 0.356 |
| | Female | 236 (44.03) | 82 (34.31) | |
| ***Age*** | <6 years old | 284 (52.99) | 141 (59.00) | 0.272 |
| | ≥6 years old | 252 (47.01) | 98 (41.00) | |
| ***Hospital delivery time*** | <5h | 290 (54.10) | 146 (38.91) | 0.207 |
| | ≥5h | 246 (45.90) | 93 (85.77) | |
| ***Nationality*** | Han nationality | 457 (85.26) | 205 (85.77) | 0.348 |
| | Ethnic minority | 79 (14.74) | 34 (14.23) | |
| ***Place of residence*** | City | 314 (58.58) | 137 (57.32) | 0.364 |
| | Country | 222 (41.42) | 102 (42.68) | |
| ***Family history*** | Yes | 182 (33.96) | 168 (70.29) | 0.109 |
| | No | 354 (66.04) | 71 (29.71) | |
| ***Only child*** | Yes | 408 (76.12) | 182 (76.16) | 0.377 |

**Table II.** Clinical data of patients [n(%)].

| | PCT (μg/L) | Cerebrospinal fluid WBC count ($\times 10^9$) | IL-6 (pg/mg) |
|---|---|---|---|
| Observation group | 1.12±0.34 | 0.004±0.002 | 7.26±1.54 |
| Control group | 0.25±0.21 | 0 | 1.34±0.82 |
| *t* | 14.53 | 11.24 | 15.67 |
| *p* | 0.029 | 0.041 | 0.021 |

**Table III.** Analysis on the sensibility and specificity of PCT and IL-6 in viral meningitis.

| | PCT | IL-6 |
|---|---|---|
| Area under the curve | 0.806 | 0.866 |
| 95% CI | 0.701~0.921 | 0.752~0.956 |
| Sensitivity | 86.81% | 81.32% |
| Specificity | 90.53% | 72.64% |

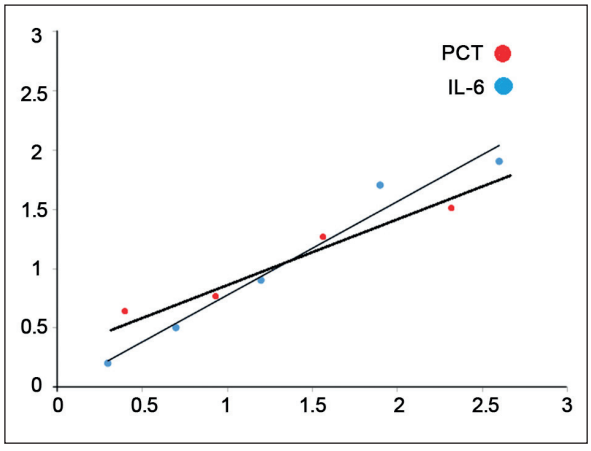


**Figure 1.** PCT and IL-6 linear correlation analysis chart. The levels of PCT and IL-6 are positively correlated with viral meningitis. The correlation degree of PCT is $r$=0.8267, and that of IL-6 is $r$=0.9234.

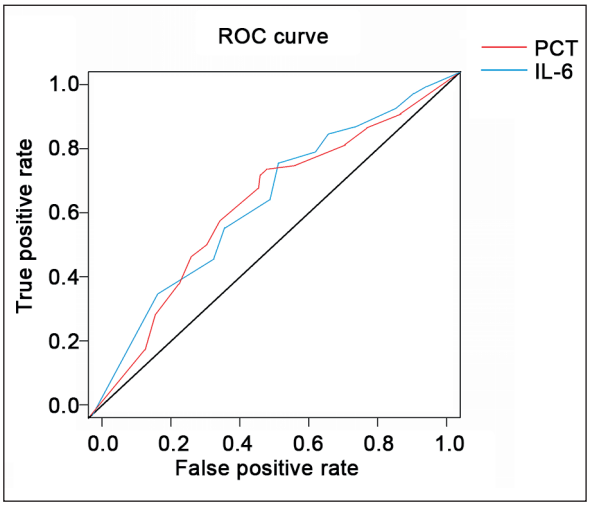


**Figure 2.** ROC curve analysis chart. The area under the curve (AUC) of PCT is 0.806, and 95% CI of PCT is 0.701-0.921. The area under the curve of IL-6 is 0.866, and 95% CI of IL-6 is 0.752-0.956.

## Discussion

PCT is a kind of living component secreted by thyroid cells and hydrolyzed by hydrolytic enzymes. It is very low or even undetectable in the serum of normal people[8]. When patients have bacterial or viral infectious diseases, PCT in serum will be significantly increased, so PLT is often used as one of reference materials to detect whether there is an inflammatory response[9]. The concentration of PLT in patients with bacterial infection diseases is increased significantly, but it is slightly increased or unchanged in viral infection. Different pathogens lead to a difference in the expression level of PCT; therefore, it is of diagnostic value and prognostic significance for meningitis caused by different pathogens to some extent[10,11]. IL-6 is a kind of inflammatory cytokine stimulated by endotoxin and interferon and secreted by endothelial cells and monocytes in patients[12]. The expression level of IL-6 in patients with inflammatory infection is generally higher than that in healthy people, but the specificity is not high. The expression level is high in various infectious diseases. Therefore, it cannot be used clinically to diagnose whether a certain disease occurs, but it can be used as an indicator for diagnosis and prognosis of infectious disease to reflect its severity [13,14]. In this paper, the expression levels of PCT and IL-6 in viral meningitis and their correlations were analyzed to explore the value of PCT and IL-6 in the diagnosis and prognosis of viral meningitis. By comparing the clinical data of patients, it can be seen that the gender, age, hospital delivery time within 10 hours, nationality, place of residence, family history, and whether the patient was an only child, had no effects on the findings. The detected levels of PCT and cerebrospinal fluid WBC, IL-6 in patients with viral meningitis were higher than those in patients with non-infectious nervous system diseases. The correlation analysis showed that PCT, IL-6 and NES were positively correlated with viral meningitis, and they were risk factors of viral meningitis. ROC curve analysis showed that the sensitivity and specificity of PCT in the detection of viral meningitis were 77.81% and 90.53%, respectively, and those of IL-6 were 81.32% and 72.64%, respectively. The reason for the increased expression level of PCT in patients with meningitis is that PCT needs to be produced by the induction of endotoxin or bacterial cytokines whereas the main pathogen of viral meningitis is a kind of virus unable to produce endotoxin autonomously. Therefore, the expression of PCT is only slightly higher than that in non-infectious patients, which agrees with Vikse et al[15]. According to Mauer et al[16], IL-6 is an interleukin widely found in the central nervous system that can strongly react with inflammatory factors of body in patients. The concentration of IL-6 in normal people is extremely low, whereas that in-patient with viral meningitis can indicate the severity of the patient's condition. It mainly exists in the matrix metalloproteinase in the form of inactive enzyme alkanes, and has a certain destructive effect on cerebral blood and spinal fluid [17,18]. At the same time, IL-6 can promote nerve cells to release stimulatory active amino acids, which can produce nitric oxide, toxic nitrogen oxides and other harmful substances, causing damage to mitochondrial function and resulting in cerebral anoxia, cranial hypertension and other injury diseases[19]. PCT and IL-6 are highly sensitive to inflammatory factors and may serve as one of the criteria for the diagnosis of brain infection diseases, but due to their low specificity, they cannot accurately diagnose pathogens. Therefore, in the clinical application, they are more appropriate to be used as an auxiliary means combined with electroencephalogram, head CT and so on, to diagnose the meningitis, which is also consistent with the findings of García-Hernández et al[20].

In this study, the expression levels of PCT and IL-6 in patients with viral meningitis were compared and their correlations were analyzed. However, due to insufficient experimental conditions, it was unable to collect multiple cases of other meningitis (such as purulent meningitis, conjunctival meningitis) to analyze the expression levels of PCT and IL-6 in meningitis of various properties, which required further study. Level of NSE in cerebrospinal fluid is an objective biochemical index that can reflect the degree of brain injury. NSE in patients with viral meningitis was significantly higher, indicating that NSE levels in cerebrospinal fluid of children with central nervous system infection are positively correlated with the severity of the disease.

## Conclusions

We observed that the levels of IL-6 and PCT, the inflammatory factors in serum, and cerebrospinal fluid of patients with viral meningitis, are slightly increased. The detection of the expression levels of IL-6 and PCT in patients with viral meningitis is of great significance for the preliminary diagnosis and rehabilitation of viral meningitis.

### Conflict of Interest

The authors have no conflicts of interest to declare.

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