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Application value of procalcitonin in patients with central nervous system infection

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Abstract. – OBJECTIVE: To study the application value of procalcitonin (PCT) in patients with central nervous system (CNS) infection.

PATIENTS AND METHODS: A total of 66 patients, including 24 patients with suppurative meningitis, 20 patients with viral meningitis and 22 patients with tuberculous meningitis, were enrolled. 20 patients admitted to the hospital due to epilepsy or headache without infection in the same period were enrolled as the control group. PCT, high-sensitivity C-reactive protein (Hs-CRP), high-sensitivity C-reactive protein (Hs-CRP), protein quantification, chloride and glucose in serum and cerebrospinal fluid, were collected.

RESULTS: The serum PCT level in suppurative meningitis group was significantly higher than that in other three groups. The dynamic monitoring of suppurative meningitis group on admission, at 72 h and 1 week after treatment showed that the serum PCT level was significantly decreased. PCT levels in cerebrospinal fluid in suppurative meningitis group, viral meningitis group and tuberculous meningitis group were decreased successively, and the differences were statistically significant. The detection of PCT in cerebrospinal fluid was more valuable than serum PCT detection in distinguishing tuberculous meningitis from viral meningitis. Continuous monitoring of changes in PCT in cerebrospinal fluid showed that there was no statistically significant difference before and after treatment. PCT level in cerebrospinal fluid was positively correlated with the serum PCT, cerebrospinal fluid white blood cell (WBC), and protein content in cerebrospinal fluid.

CONCLUSIONS: The dynamic changes of serum PCT in patients with suppurative meningitis can be used to evaluate the disease, guide the clinical medication, and monitor the prognosis.

Key Words
Procalcitonin (PCT), Central nervous system infection, Suppurative meningitis, Tuberculous meningitis, Viral meningitis.

Introduction

Central nervous system (CNS) infection is the acute and chronic inflammatory (or non-inflammatory) disease caused by the invasion of a variety of biological pathogens against the brain or spinal cord parenchyma, membranes and blood vessels, which is one of the common diseases of neurology[1-3]. The prevalence rates of suppurative meningitis, tuberculous meningitis and viral meningitis are higher. Clinical symptoms of the above three kinds of CNS infections have a certain similarity in the early stage of disease, making the diagnosis and differential diagnosis of disease difficult. If the diagnosis and treatment are offered in time, severe sequelae can be caused[4-8]. The early definite diagnosis and timely identification of disease, on the one hand, have a decisive significance in increasing the treatment level and improving the prognosis. On the other hand, it avoids the risk of drug-resistant bacterial infection caused by the abuse of antibiotics. Procalcitonin (PCT) is a new laboratory index developed in recent years and has been widely concerned by scholars in China and foreign countries[9-12]. It has important values in the diagnosis, differential diagnosis, treatment and prognostic evaluation of bacterial infection[13,14]. Compared with other inflammatory factors, PCT is more sensitive to the inflammatory response with a longer duration, which can be detected in the serum 4 h after infection, and returns to normal in 2-3 days; PCT is not susceptible to other factors (such as renal insufficiency, low immunity and viral infection). Under normal circumstances, serum PCT content is very low and undetectable; when virus infection or non-infectious disease occurs, serum PCT level does not rise or only rises slightly; when severe bacterial

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infection occurs, serum PCT level is positively correlated with the degree of inflammatory response and fatality rate, which returns to normal with the inflammation control and recovery of disease. Recent studies[5] have shown that serum PCT detection has a certain value in the differential diagnosis of CNS infection. However, the study on the relationship between PCT content in cerebrospinal fluid and CNS infection is still in the initial stage, and there are also many controversies. This study discussed the application value of PCT in diagnosis, differential diagnosis and curative effect observation of CNS infection through measuring the PCT levels in serum and cerebrospinal fluid in CNS infected patients.

Patients and Methods

Patients

A total of 66 patients (24 patients with suppurative meningitis, 20 patients with viral meningitis and 22 patients with tuberculous meningitis) with an average age of 40.21 years diagnosed as acute encephalitis and meningitis admitted into the Infection Department of our hospital from January 2014 to December 2016 were selected as the observation group. Diagnostic criteria: traditional clinical methods, such as cerebrospinal fluid routine, biochemistry, acid-fast staining, cytology, blood culture, blood routine, electroencephalogram and head imaging examinations. A total of 20 patients with an average age of 43.05 years admitted into the hospital due to epilepsy or headache without infection in the same period were screened as a control group. Signed written informed consents were obtained from all participants before the study.

This study was approved by the Ethics Committee of the Affiliated Hospital of Beihua University. Signed written informed consents were obtained from all participants before the study.

Data Collection

Measured values of PCT in serum and cerebrospinal fluid in objects of study on admission were collected, and PCT levels in serum and cerebrospinal fluid in patients in each group at 72 h and 1 week after treatment were measured. Other test data, such as WBC in peripheral blood, Hs-CRP, WBC in cerebrospinal fluid, protein quantification, chloride and glucose, were collected. PCT was detected using enzyme-linked immunosorbent assay (microplate reader: TECN-CAN, Vienna, Austria). The normal reference range of PCT was set as PCT<0.5 ng/ml.

Statistical Analysis

All statistics were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). *t*-test was performed for the comparison of mean value, X^2 test for the rate between groups. Spearman analysis was used to evaluate the relationship between PCT concentration and other traditional indexes. $p<0.05$ suggested statistical significance.

Results

General Conditions

There were 66 patients in observation group (24 patients in suppurative meningitis group, 20 patients in virus meningitis group and 22 in tuberculous meningitis group), including 37 males and 29 females with an average age of (40.21±3.59) years. There were 20 patients in control group, including 11 males and 9 females with an average age of (43.05±4.68) years. No significant difference was observed in gender and age between the two groups.

Traditional Inflammatory Indexes

Blood WBC level in suppurative meningitis group was significantly increased than that in control group, tuberculous meningitis group and viral meningitis group ($p<0.05$). However, no significant difference existed between tuberculous meningitis group and viral meningitis group. CRP level in suppurative meningitis group, tuberculous meningitis group, and viral meningitis group was significantly increased compared with that in control group ($p<0.05$), and CRP level in tuberculous meningitis group and viral meningitis group was less than that in suppurative meningitis group. WBC in cerebrospinal fluid in control group, viral meningitis group, tuberculous meningitis group, and suppurative meningitis group, showed a gradual increasing trend. The differences among groups were statistically significant ($p<0.05$). Glucose levels in suppurative meningitis group and tuberculous meningitis group were lower than those in viral meningitis group and control group ($p<0.05$), and the differences between suppurative meningitis group and tuberculous meningitis group, viral meningitis group and control group were not statistically significant. The protein level in cerebrospinal fluid in suppurative meningitis group was

Table I. Traditional inflammatory indexes of each group on admission.

	Suppurative meningitis group	Tuberculous meningitis group	Viral meningitis group	Control group
Serum WBC (10^9/L)	11.02±8.04#	5.82±1.81*	4.64±1.48*	4.81±1.36
Serum CRP (mg/dL)	70.99±50.35#	20.68±5.46#*	15.69±8.27#*	1.88±1.19
Cerebrospinal fluid WBC (10^9/L)	567.82±485.56#	106.22±73.42#*	74.30±59.87#*	3.34±3.32
Cerebrospinal fluid protein (g/L)	1.50±0.78#	1.02±0.39#*	0.50±0.17*°	0.31±0.12
Cerebrospinal fluid chloride (mmol/L)	112.74±7.20#	114.58±6.50#	78.36±57.89*°	121.09±1.92
Cerebrospinal fluid glucose (mmol/L)	1.68±0.55#	1.92±0.36#	2.43±0.37*°	2.43±0.58

Note: #$p<0.05$ in comparison with control group; *$p<0.05$ in comparison with suppurative meningitis group; °$p<0.05$ in comparison with tuberculous meningitis group.

significantly increased compared with that in tuberculous meningitis group ($p<0.05$), and levels of the two groups were higher than those in viral meningitis group and control group ($p<0.05$); there was no significant difference between viral meningitis group and control group. Chloride levels in cerebrospinal fluid in suppurative meningitis group and tuberculous meningitis group were significantly lower than those in control group and viral meningitis group ($p<0.05$), and there were no statistically significant differences between suppurative meningitis group and tuberculous meningitis group, viral meningitis group and control group (Table I).

Serum PCT Levels of Each Group on Admission, at 72 h and 1 Week After Treatment

Serum PCT level in each experimental group was higher than that in control group, among which serum PCT level in suppurative meningitis group was increased most significantly, and was significantly higher than that in viral meningitis group and tuberculous meningitis group ($p<0.05$, Table II). The dynamic monitoring of suppurative meningitis group on admission, at 72 h and 1 week after treatment showed that the serum PCT level was significantly decreased ($p<0.05$, Table II). The dynamic monitoring of viral meningitis and tuberculous meningitis on admission, at 72 h and 1 week after treatment showed that the serum PCT level had no statistically significant differences ($p>0.05$, Table II).

PCT Levels in Cerebrospinal Fluid in Each Group on Admission, at 72 h and 1 Week After Treatment

PCT level in cerebrospinal fluid in each experimental group was significantly higher than that in control group. Cerebrospinal fluid PCT levels of suppurative meningitis group, viral meningitis group and tuberculous meningitis group were decreased successively, besides, the difference between each group was statistically significant ($p<0.05$, Table III). The detection of PCT in cerebrospinal fluid was more valuable than serum PCT detection in distinguishing tuberculous meningitis from viral meningitis. Continuous monitoring of changes in PCT in cerebrospinal fluid in suppurative meningitis group, viral meningitis group, and tuberculous meningitis group showed that there was no statistically significant difference before and after treatment, although PCT was also decreased gradually with the treatment ($p<0.05$, Table III).

Table II. Serum PCT levels on admission, at 72 h and 1 week after treatment.

	Suppurative meningitis group	Tuberculous meningitis group	Viral meningitis group	Control group
On admission	8.72±2.10#	0.44±0.22*	0.38±0.16*	0.05±0.003
After 72 h treatment	6.02±0.77°	0.38±0.19	0.25±0.06	0.05±0.002
After 1 week treatment	1.63±0.69°	0.31±0.16	0.21±0.04	0.04±0.005

Note: #<0.05 in comparison with control group; *$p<0.05$ in comparison with suppurative meningitis group; °$p<0.05$ in comparison with serum PCT level on admission.

Table III. PCT levels in cerebrospinal fluid on admission, at 72 h and 1 week after treatment.

	Suppurative meningitis group	Tuberculous meningitis group	Viral meningitis group	Control group
On admission	0.72±0.32#	0.39±0.20#*	0.16±0.11#*°	0.04±0.03
After 72 h treatment	0.68±0.35	0.35±0.18	0.15±0.13	0.04±0.02
After 1 week treatment	0.59±0.41	0.30±0.22	0.12±0.11	0.03±0.03

Note: #$p<0.05$ in comparison with control group; *$p<0.05$ in comparison with suppurative meningitis group; °$p<0.05$ in comparison with tuberculous meningitis group.

Analysis of Correlation Between PCT in Cerebrospinal Fluid and Other Indexes

The correlation analysis of PCT in cerebrospinal fluid and serum PCT, blood WBC, CRP, WBC in cerebrospinal fluid, protein in cerebrospinal fluid, chloride and glucose quantification showed that PCT level in cerebrospinal fluid was positively correlated with the serum PCT (OR=0.883, $p<0.05$), WBC in cerebrospinal fluid (OR=0.879, $p<0.01$) and protein content in cerebrospinal fluid (OR=0.784, $p<0.05$) (Table IV).

Discussion

CNS infection has different classifications according to the pathogenic microorganism, diseased region and severity of disease, and the timely diagnosis and correct treatment are the keys to reduce the mortality and morbidity of disease[1-3]. At present, the golden standard of diagnosis is the pathogenic detection of cerebrospinal fluid, but it is the invasive and time-consuming operation, so it has limited guiding significance for the early clinical treatment. Cerebrospinal fluid examination plays an irreplaceable role in the diagnosis of CNS diseases; in typical suppurative meningitis, WBC in cerebrospinal fluid is increased due to the stimulation of bacteria and its metabolites against the meninges; in CNS infection, Blood-brain barrier (BBB) is destroyed, so the protein content in cerebrospinal fluid is increased compared with the normal content. BBB is destroyed significantly in suppurative meningitis, so the protein content in cerebrospinal fluid is increased obviously. BBB is destroyed slightly in viral meningitis, so the protein content in cerebrospinal fluid is not increased obviously compared with that in suppurative meningitis[1]. In viral meningitis, cells are destroyed and release glucose glycolysis enzyme, thus reducing the glucose content in cerebrospinal fluid, but there is no significant change in viral meningitis. The results of this study were consistent with the above changes in cerebrospinal fluid.

Table IV. Correlation analysis between PCT in cerebrospinal fluid and other indexes.

	OR	p
Serum PCT (ng/ml)	0.883	<0.001
Serum WBC (*10^9/L)	0.742	0.41
Serum CRP (mg/dL)	0.639	0.35
Cerebrospinal fluid WBC (*10^9/L)	0.879	<0.001
Cerebrospinal fluid protein (g/L)	0.784	<0.001
Cerebrospinal fluid chloride (mmol/L)	0.711	0.16
Cerebrospinal fluid glucose (mmol/L)	0.737	0.09

Note: p<0.05 suggested statistical significance.

Over the years, scholars have been committed to finding reliable laboratory indicators, but some indicators, including peripheral WBC, CRP, IL-6, IL-8 and TNF-α, fail to obtain the satisfactory effects[15]. Studies have shown that serum PCT can be used in the early diagnosis of suppurative meningitis and differential diagnosis of different meningitis, which has a certain value in helping guide the early application of antibiotics, improving the survival rate and determining the therapeutic effect[5,13,14]. However, there are fewer studies on the cerebrospinal fluid PCT in China and other countries, and the sample size is relatively small, so the value of cerebrospinal fluid PCT is still very controversial. Some researchers suggest that cerebrospinal fluid PCT has the same treatment and guidance values as the serum PCT. With the improvement of the disease, cerebrospinal fluid PCT level continues to decline, and the continuous high level of cerebrospinal fluid PCT often indicates the serious condition and poor prognosis. Kepa et al[16]

collected the PCT in blood and cerebrospinal fluid in patients with intracranial infection and thought that cerebrospinal fluid PCT has poor sensitivity in the differential diagnosis of CNS, compared with serum PCT, they still have important value in the assessment of disease and prognosis of patients with bacterial intracranial infection. In this work, monitoring serum and cerebrospinal fluid PCT levels in CNS infection has a better identification effect, among which serum PCT detection is suitable for identification of suppurative meningitis, tuberculous meningitis and viral meningitis; cerebrospinal fluid PCT concentration detection may be more conducive to the identification of tuberculous meningitis and viral meningitis.

The increased serum PCT level in patients with bacterial intracranial infection may be due to a series of biochemical reactions released into the blood induced by bacterial endotoxin and cytokines, etc. Studies have shown that bacterial endotoxin is an important factor of inducing PCT[9-11]. Virus and mycobacterium tuberculosis cannot produce endotoxin, so they cannot or can only slightly increase the PCT level. Compared with serum PCT, PCT in cerebrospinal fluid is not increased significantly[5,6,8]. Previous studies have found that the blood brain barrier in patients with suppurative meningitis and tuberculous meningitis is severer than that in patients with viral meningitis. This experiment found that the PCT in cerebrospinal fluid in viral meningitis and tuberculous meningitis groups were increased than that in viral meningitis group significantly, suggesting that the source of PCT in cerebrospinal fluid is related to the damage of blood brain barrier, and its content change is linearly related to protein content and WBC in cerebrospinal fluid, which also supports the conclusion.

The dynamic monitoring of suppurative meningitis group on admission, at 72 h and 1 week after treatment, showed that the serum PCT level was significantly decreased; the serum PCT levels in viral meningitis group and tuberculous meningitis group had no statistically significant difference. PCT in cerebrospinal fluid in each group on admission, at 72 h and 1 week after treatment had no statistically significant difference, suggesting that the serum PCT level can be used to predict the severity of bacterial intracranial infection, guide the medication, and determine the course of treatment; the higher the PCT value is, the severer the disease will be and the poorer the prognosis will also be. Relatively speaking, PCT in cerebrospinal does not have clinical significance for CNS infection. It was also found in this experiment that when the blood PCT in some patients with suppurative meningitis were normal, cerebrospinal fluid examination was not necessarily normal, which may be related to the slow recovery of each index of cerebrospinal fluid. Therefore, the normal blood PCT value cannot be the indication for drug discontinuance for patients with suppurative meningitis, and the full course of treatment should still be offered.

Conclusions

The detection of serum and cerebrospinal fluid PCT levels contributes to the diagnosis and differential diagnosis of suppurative meningitis, virus meningitis and tuberculous meningitis. Dynamic detection of serum PCT changes can be used to observe the drug effect and guide the clinical application of antibacterial agents.

Conflict of Interest:
The Authors declare that they have no conflict of interests.

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