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Original Article

Diagnostic value of CRP, PCT and TNF-α levels in serum and cerebrospinal fluid for purulent meningitis and viral meningitis

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Abstract: Objective: To investigate the diagnostic value of serum and cerebrospinal fluid (CSF) levels of C reactive protein (CRP), procalcitonin (PCT) and tumor necrosis factor-α (TNF-α) for purulent meningitis and viral meningitis. Methods: A total of 147 children with meningitis admitted to The Affiliated Hospital of Southwest Medical University were retrospectively evaluated, including 76 cases of viral meningitis and 71 cases of purulent meningitis. Another 50 children without meningitis within the same period were selected as the control group. The CSF and serum levels of CRP, PCT and TNF-α were measured upon admission and during the recovery period, and compared between two groups. Results: On admission, the serum and CSF levels of CRP, PCT and TNF-α in the viral meningitis and purulent meningitis groups were significantly higher than those in the control group ($P<0.05$), while the serum and CSF levels of CRP, PCT and TNF-α of patients in the purulent meningitis group were significantly higher than those in the viral meningitis group ($P<0.05$). The area under the Receiver Operator Characteristic (ROC) curve was 0.958 and 0.921 respectively for combined detection of serum levels of CRP, PCT and TNF-α in the diagnosis of purulent meningitis. After treatment, the serum and CSF levels of CRP, PCT and TNF-α in viral meningitis and purulent meningitis groups were lower than those before treatment ($P<0.05$), while no significant difference was noted in serum and CSF levels of CRP, PCT and TNF-α between the two meningitis groups ($P>0.05$). Conclusion: The serum and CSF levels of CRP, PCT and TNF-α in children with purulent meningitis are higher than those in children with viral meningitis, and the combined detection of CRP, PCT and TNF-α in serum and CSF has certain significance in the differential diagnosis of purulent meningitis and viral meningitis.

Keywords: Purulent meningitis, viral meningitis, C reactive protein, procalcitonin, tumor necrosis factor-α, diagnostic value

Introduction

Infection of the central nervous system (CNS) is frequently seen in clinical practice, and the related patients are clinically categorized as severe cases due to high mortality and disability rates. According to a survey by the World Health Organization in 2010, the global incidence rate of meningitis in children is 10.5 to 12.3 cases per 100,000, of which the mortality rate is up to 30% and one-third of the survivors have different degrees of disability [1, 2]. The pathogens causing CNS infections in children include bacteria, viruses, fungi, and rickettsia etc., of which bacteria and virus are the most common pathogens [3, 4]. Clinical studies have found that viral meningitis and purulent meningitis are quite similar in clinical symptoms, but differ greatly in treatments and prognosis. Therefore, early differential diagnosis of the two types of infections is important for treatment and prognosis in children [5-7].

C-reactive protein (CRP) is an important index of human infection [8]. Procalcitonin (PCT) is one of the indices reflecting the severity of human infection, which is also sensitive to viral infection and can rapidly increase after infection [9]. Studies have found that a certain amounts of PCT can stimulate immunoglobulin to exert anti-infective effects, but its excessive expression can cause inflammatory reactions, resulting in damage to the body [10]. In addition, during CNS infection, pathogens that cro-

ss the blood-brain barrier can not only damage brain tissue, but also directly stimulate TNF-α (one of the proinflammatory factors), and increase its expression rapidly [11]. Therefore, in this study, patients with viral meningitis and purulent meningitis were studied and monitored for CSF and serum levels of CRP, PCT and TNF-α, in order to explore the value of the three indices in the differential diagnosis of purulent meningitis and viral meningitis, which were reported as follows.

Materials and methods

General data

A retrospective study was conducted in 147 children with meningitis admitted to the Department of Pediatrics in The Affiliated Hospital of Southwest Medical University from April 2017 to April 2020, including 76 children with viral meningitis (42 males and 34 females, 1-13 years of age), and 71 children with purulent meningitis (43 males and 28 females, 1-11 years of age). In the meantime, another 50 children without meningitis within the same period were selected as the control group (27 males and 23 females, 1-12 years of age). All children included in this study had an informed consent form signed by their parents. This study was approved by the Ethics Committee of The Affiliated Hospital of Southwest Medical University.

Inclusion and exclusion criteria

Inclusion criteria: (1) patients met the diagnostic criteria for viral meningitis in the 2010 *Zhu Futang Practical Pediatrics* [12]; (2) patients were aged between 1-14 years old; (3) patients were with confirmed viral meningitis or purulent meningitis for the first time; (4) patients with complete clinical information.

Exclusion criteria: (1) severe malnutrition, and tumors; (2) tuberculous meningitis; (3) or other infections.

Methods

Determination of CRP, PCT and TNF-α: Venous blood samples (5 mL) from patients were collected and stored in EDTA tubes upon admission and during the recovery period. After being stored at 4°C for 15 minutes in the refrigerator, the samples were centrifuged at 3,300 rpm/min using a centrifuge, the separated plasma was mixed with phosphate buffer solution containing 40 mL protease inhibitors, and was kept in the freezer at -80°C. Then the levels of CRP, PCT and TNF-α were measured by enzyme-linked immunosorbent assay (Shanghai Enzyme-linked Biotechnology Co., Ltd., China, cat. nos. ml057570, ml026011 and ml0773-85) using an automatic multifunctional microplate reader (Thermo, USA). Cerebrospinal fluid samples were obtained by lumbar puncture and stored at -70°C for measurement of the CRP, PCT and TNF-α levels using enzyme-linked immunosorbent assay (ELISA). Procedural steps were performed in strict accordance with the instruction manuals.

Statistical analysis

SPSS 17.0 statistical software was used for statistical analysis. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. For measurement data, those conforming to a normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ± sd), those satisfying homogeneity of variances were examined using the independent-samples t-test (t), and those violating normal distribution and homogeneous variances were evaluated using Wilcoxon rank sum test (z). Enumeration data were presented as number of cases or percentage (n, %), and were examined by chi-square test (χ^2). SPSS 22.0 statistical software was adopted to draw the ROC curve and calculate the area under the ROC curve (AUROC). A 95% confidence interval (95% CI) was used, and *P* value of less than 0.05 was considered statistically significant.

Results

Comparison of general data among the three groups

There was no significant difference in sex, age, onset time, pediatric critical score and Glasgow coma score upon admission among three groups (P>0.05). See **Table 1**.

Comparison of serum levels of CRP, PCT and TNF-α on admission among the three groups

There were statistical differences in serum CRP, PCT and TNF-α levels upon admission among three groups (P<0.05). Further pairwise

Table 1. Comparison of general data among three groups

Characteristics	Viral meningitis group (n=76)	Purulent meningitis group (n=71)	Control group (n=50)	$F/\chi^2/t$	P
Gender (male/female)	42/34	43/28	29/21	0.423	0.809
Age (years)	6.3±2.6	6.5±2.7	6.4±2.9	0.890	0.116
Onset time (h)	21.00±8.90	22.03±10.43		0.654	0.520
Pediatric critical score (points)	67.98±3.98	68.68±4.76		0.970	0.334
Glasgow coma score (GCS) on admission (points)	6.36±1.41	6.41±1.63		0.199	0.842

Table 2. Comparison of serum levels of CRP, PCT and TNF-α on admission among three groups

Group	CRP (mg/L)	PCT (ng/mL)	TNF-α (pg/mL)
Viral meningitis group (n=76)	15.16±4.78$^{***,\#\#\#}$	0.58±0.11$^{**,\#\#\#}$	14.92±3.98$^{***,\#\#\#}$
Purulent meningitis group (n=71)	19.08±8.65***	1.32±0.63***	17.64±5.23***
Control group (n=50)	6.95±2.03	0.32±0.09	6.54±0.92
F-value	59.252	114.491	116.534
P	<0.001	<0.001	<0.001

Note: **P<0.01 and ***P<0.001 as compared with control group; $^{\#\#\#}$P<0.001 as compared with purulent meningitis group. CRP: C reactive protein; PCT: procalcitonin; TNF-α: tumor necrosis factor-α.

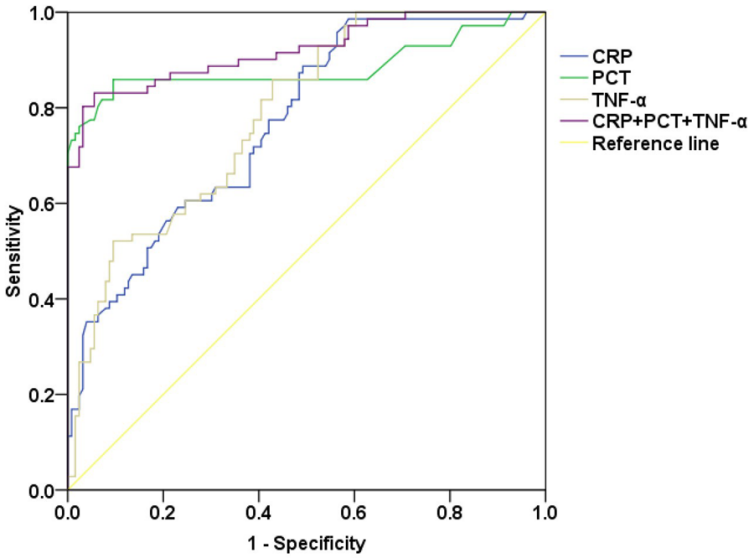

Figure 1. ROC curve for serum levels of CRP, PCT and TNF-α on admission in diagnosing purulent meningitis. CSF: serum and cerebrospinal fluid; CRP: C reactive protein; PCT: procalcitonin; TNF-α: tumor necrosis factor-α; ROC: Receiver Operator Characteristic.

comparison revealed that serum CRP, PCT and TNF-α levels in the viral meningitis and purulent groups were higher than those in the control group; while serum CRP, PCT and TNF-α levels in the purulent meningitis group were higher than those in the viral meningitis group, and the differences were all statistically significant (P<0.05). See **Table 2**.

Diagnostic value of serum CRP, PCT and TNF-α levels for purulent meningitis upon admission

The area under the ROC curve was 0.862 for serum level of CRP in the diagnosis of purulent meningitis, and the cutoff value of serum CRP was 16.21 mg/L with Youden index, specificity, and sensitivity of 0.362, 0.770, and 0.592, respectively. The area under the ROC curve was 0.717 for serum level of PCT in the diagnosis of purulent meningitis, and the cutoff value of serum PCT was 0.66 ng/mL with Youden index, specificity, and sensitivity of 0.890, 0.895, and 0.905, respectively. The area under the ROC curve was 0.890 for serum level of TNF-α in the diagnosis of purulent meningitis, and the cutoff value of serum TNF-α was 17.73 pg/mL with Youden index, specificity, and sensitivity of 0.426, 0.521, and 0.905, respectively. The area under the ROC curve was 0.958 for combined detection of three indices in the diagnosis of purulent meningitis. See **Figure 1**.

Table 3. Comparison of CSF levels of CRP, PCT and TNF-α on admission among three groups

Group	CRP (mg/L)	PCT (ng/mL)	TNF-α (pg/mL)
Viral meningitis group (n=76)	2.38±0.63$^{**,\#\#\#}$	0.10±0.03$^{**,\#\#\#}$	7.02±1.23$^{***,\#\#\#}$
Purulent meningitis group (n=71)	3.42±1.12***	0.20±0.13***	11.23±3.76***
Control group (n=50)	0.32±0.12	0.05±0.02	4.36±0.78
F-value	223.724	50.083	126.148
P	<0.001	<0.001	<0.001

Note: **P<0.01 and ***P<0.001 as compared with control group; $^{\#\#\#}$P<0.001 as compared with purulent meningitis group. CSF: serum and cerebrospinal fluid; CRP: C reactive protein; PCT: procalcitonin; TNF-α: tumor necrosis factor-α.

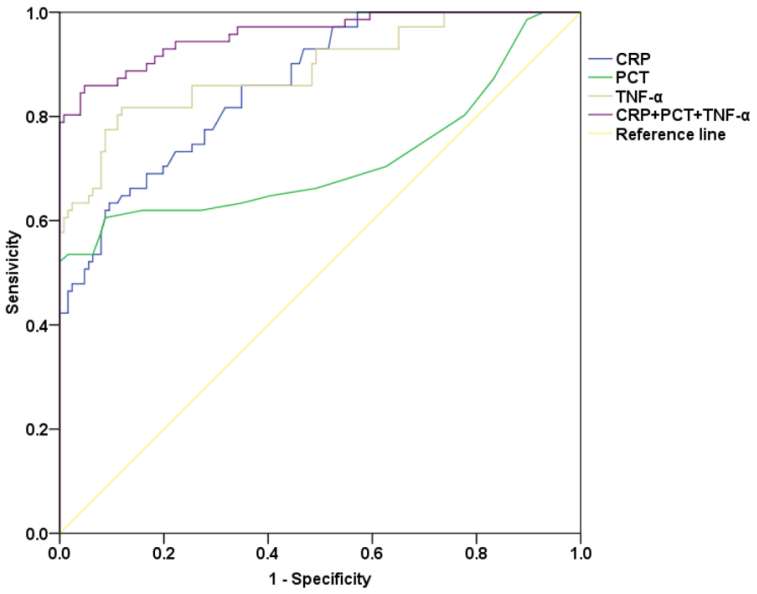

Figure 2. ROC curve for CSF levels of CRP, PCT and TNF-α on admission in diagnosing purulent meningitis. CSF: serum and cerebrospinal fluid; CRP: C reactive protein; PCT: procalcitonin; TNF-α: tumor necrosis factor-α; ROC: Receiver Operator Characteristic.

Comparison of CSF levels of CRP, PCT and TNF-α on admission among the three groups

There were statistically significant differences in CSF levels of CRP, PCT and TNF-α upon admission among three groups (P<0.05). Further pairwise comparison showed that CSF levels of CRP, PCT and TNF-α in the viral meningitis group were higher than those in the control group, while CSF levels of CRP, PCT and TNF-α in the purulent meningitis group were higher than those in the viral meningitis group, and the difference was statistically different (P< 0.05). See **Table 3**.

Diagnostic value of CSF levels of CRP, PCT and TNF-α on admission for purulent meningitis

The area under the ROC curve was 0.768 for CSF level of CRP in the diagnosis of purulent meningitis, and the cutoff value of CSF CRP was 2.83 mg/L with Youden index, specificity, and sensitivity of 0.539, 0.905, and 0.634, respectively. The area under the ROC curve was 0.885 for CSF level of PCT in the diagnosis of purulent meningitis, and the cutoff value of CSF CRP was 0.18 ng/mL with Youden index, specificity, and sensitivity of 0.521, 0.984, and 0.521, respectively. The area under the ROC curve was 0.787 for CSF level of TNF-α in the diagnosis of purulent meningitis, and the cutoff value of CSF TNF-α was 8.02 pg/mL with Youden index, specificity, and sensitivity of 0.688, 0.913, and 0.775, respectively. The area under the ROC curve was 0.921 for combined detection of three indices in the diagnosis of purulent meningitis. See **Figure 2**.

Comparison of serum and CSF levels of CRP, PCT and TNF-α upon admission and during the recovery period after treatment

After treatment, serum and CSF levels of CRP, PCT and TNF-α decreased in both purulent meningitis and viral meningitis groups as compared with those on admission, and the differences were all statistically significant (P< 0.05). However, no difference was observed between two groups concerning serum and CSF levels of CRP, PCT and TNF-α after treatment (P>0.05). See **Tables 4** and **5**.

Discussion

Previous studies have shown that patients with viral meningitis often develop symptoms

Table 4. Comparison of serum levels of CRP, PCT and TNF-α before and after treatment in two groups

Characteristics	Viral meningitis group (n=76)	Purulent meningitis group (n=71)	t	P
CRP (mg/L)				
On admission	15.16±4.78	19.08±8.65	3.432	<0.001
After treatment	4.80±1.74***	4.57±1.48***	0.860	0.391
PCT (ng/mL)				
On admission	0.58±0.11	1.32±0.63	10.080	<0.001
After treatment	0.34±0.11***	0.35±0.13***	0.505	0.615
TNF-α (pg/mL)				
On admission	14.92±3.98	17.64±5.23	3.563	<0.001
After treatment	6.51±1.78***	6.49±1.89***	0.066	0.947

Note: ***P<0.001 as compared with that on admission. CRP: C reactive protein; PCT: procalcitonin; TNF-α: tumor necrosis factor-α.

Table 5. Comparison of CSF levels of CRP, PCT and TNF-α before and after treatment in two groups

Characteristics	Viral meningitis group (n=76)	Purulent meningitis group (n=71)	t	P
CRP (mg/L)				
On admission	2.38±0.63	3.42±1.12	6.997	<0.001
After treatment	0.35±0.11***	0.36±0.12***	0.527	0.599
PCT (ng/mL)				
On admission	0.10±0.03	0.20±0.13	6.542	<0.001
After treatment	0.05±0.03***	0.05±0.04***	0.012	0.982
TNF-α (pg/mL)				
On admission	7.02±1.23	11.23±3.76	9.248	<0.001
After treatment	4.32±0.79***	4.38±0.83***	0.449	0.654

Note: ***P<0.001 as compared with that on admission. CSF: serum and cerebrospinal fluid; CRP: C reactive protein; PCT: procalcitonin; TNF-α: tumor necrosis factor-α.

of viral diarrhea in the early stage, and viral pathogens causing the infection are mostly human astrovirus, calicivirus, enteric adenovirus, and echovirus that can cause outbreaks [13, 14]. For purulent meningitis, the main pathogens are Escherichia coli and group B streptococcus [15]. Although the two infections have similar clinical symptoms, their treatment options vary greatly due to different pathogenic factors. Therefore, early differential diagnosis is important for later treatment and prognosis.

C-reactive protein (CRP) is a protein synthesized in the liver under the influence of inflammatory factors such as interleukin 6, CRP is a more commonly used index for detection in clinical practice [16]. When the human body is under inflammatory stimulations and injury stress, CRP exhibits significantly elevated expression in the blood [17]. It has been shown that stimulation of inflammation and cytokines can increase blood-brain barrier permeability [18]. In this study, it was also found that CRP levels were increased in both serum and cerebrospinal fluid after central nervous system infection, and the increase was more pronounced in children with purulent meningitis.

Clinical studies on procalcitonin (PCT) found that PCT starts to rise in the initial stage of the infection and increases earlier than other inflammatory factors [19]. Some studies showed that PCT level is consistent with the severity of infection, and it increases significantly both in bacterial infections and in viral infections [20, 21]. In healthy individuals, the serum and CSF levels of PCT are very low (<0.05 ng/mL), but generally begin to rise at 2 hours and peaks at 12-24 hours after infection, without interference from the use of hormones and antibiotics, which are of great significance for efficacy evaluation, prognosis prediction and disease differentiation [22]. In this study, it was also found that serum and CSF levels of PCT in the purulent meningitis group were higher than those in the viral meningitis group, indicating that PCT has higher specificity in the diagnosis of purulent meningitis caused by bacteria.

Studies have shown that inflammatory factors are involved in all stages of viral infection [23]. In a study on tumor necrosis factor-α (TNF-α), it was found that TNF-α has dual biological effects, can resist infection at low concentration, and participates in the regulation of inflammatory responses in tissue repair. However, high TNF-α levels can cause damage to the immune system, which will activate neutrophils, enhance leukocyte phagocytosis, and promote secretion of inflammatory factors, fur-

ther increasing vascular permeability and promoting the production of TNF-α during bacterial infection [24]. Studies on TNF-α in patients with viral meningitis have demonstrated that TNF-α has complicated mechanisms of action: generally, viral stimulation promotes glial cells to produce interleukin-1 (IL-1) which further generates TNF-α, which exhibits a local cytotoxic activity and enhances the biological effect of endotoxins, thus inducing directly and indirectly causing damage to brain tissue [25]. In addition, study has shown that TNF-α level in CSF is significantly increased in patients with bacterial meningitis and viral meningitis in the acute stage [26]. In this study, we also found that TNF-α was increased in both serum and CSF after CNS infection, and the increase was more obvious in the purulent meningitis group.

In the differential diagnosis of diseases, study has shown that the effective rate of differential diagnosis using combined cytological and biochemical tests is 52.4-63.8% in patients with CNS infection [27]. In our study, the area under ROC curve was 0.958 for combined detection of serum levels of CRP, PCT and TNF-α in the diagnosis of purulent meningitis, while the area under ROC curve was 0.921 for combined detection of CSF levels of CRP, PCT and TNF-α in the diagnosis of purulent meningitis. All these indices are of high diagnostic value. However, there are several limitations to this study, including a small sample size, being a single-center investigation and retrospective in nature. Therefore, multi-center studies with lager sample size and prospective design are needed in the future to deeply explore action mechanism of CRP, PCT and TNF-α in meningitis.

Effective treatment and comprehensive nursing management and monitoring can significantly improve life quality and prognosis of children [28]. Our further study on CRP, PCT and TNF-α levels in the recovery period after treatment has revealed that the levels of CRP, PCT and TNF-α decreased in both experimental groups after treatment compared with those before treatment.

In conclusion, the levels of CRP, PCT and TNF-α in serum and CSF of children with purulent meningitis are higher than those of children with viral meningitis, and the combined detection of CRP, PCT and TNF-α in serum and CSF has certain clinical significance in differentiating between purulent meningitis and viral meningitis.

Disclosure of conflict of interest

None.

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