Clinical Biochemistry xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Direct comparison of the diagnostic accuracy between blood and cerebrospinal fluid procalcitonin levels in patients with meningitis

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ARTICLE INFO

Article history:
Received 6 May 2015
Received in revised form 23 June 2015
Accepted 24 June 2015
Available online xxxx

Keywords:
Meningitis
PCT
CSF
Biomarker

ABSTRACT

Objective: To compare the clinical utility of serum and cerebrospinal fluid (CSF) procalcitonin (PCT) for the diagnosis of bacterial meningitis (BM) among patients with suspected meningitis.

Methods: Patients with meningitis-like symptoms (n = 120), admitted to the Second People's Hospital of Wuxi or the Changhai Hospital of Shanghai between January 2011 and December 2013, were prospectively and consecutively enrolled in this study. BM was finally diagnosed by CSF culture, Gram staining, quantitative polymerase chain reaction (qPCR), and treatment response. The diagnostic accuracy of the serum and CSF PCT was assessed by receiver operator characteristic (ROC) curve analysis. The relationship between CSF and serum PCT levels as well as the CSF leukocyte count and protein level was analyzed by Spearman's correlation analysis.

Results: PCT level in both the serum and CSF was significantly increased in the BM patients. The area under ROC curve of serum PCT for the diagnosis of BM was 0.96 (95% confidence interval (CI): 0.93–1.00), significantly higher than that of CSF PCT (0.90, 95% CI: 0.83–0.96). Using 0.88 ng/mL as the threshold, the diagnostic sensitivity, specificity, and accuracy of serum PCT for the diagnosis of BM were 0.87 (95% CI, 0.73–0.95), 1.00 (95% CI, 0.95–1.00), and 95%, respectively. The serum PCT level was positively correlated with the CSF PCT level, leukocyte count, and protein level.

Conclusion: Both the serum and CSF PCT had a high diagnostic value for BM among suspected meningitis patients, and serum PCT demonstrated a superior diagnostic value compared to CSF PCT.

1. Introduction

Bacterial meningitis (BM) remains a common infectious disease with high mortality and constitutes a major medical concern to public health worldwide [1–3]. To a large extent, clinical manifestations among BM and viral meningitis, tuberculous meningitis, and fungal meningitis are similar; however, different treatment approaches are required for different pathogens. Thus, an early and accurate differential diagnosis is crucial [4,5]. Generally, the diagnosis of BM relies on microbiological tests and laboratory findings. Identifying of pathogens by cerebrospinal fluid (CSF) bacterial culture and Gram staining is highly specific; however, the sensitivity of bacterial culture and staining techniques is low as it has been reported that nearly half of BM patients had negative microbiological findings [6,7]. In addition, microbiological examination is time consuming, which makes an early diagnosis impossible. Analysis of leukocyte count and protein level in CSF is an alternative method for diagnosing BM, although the sensitivity and specificity are not high enough to differentiate BM from viral meningitis, tuberculous meningitis, or fungal meningitis [7,8]. Therefore, it is necessary to identify more sensitive and specific biomarkers for the diagnosis of BM.

In recent decades, procalcitonin (PCT), a polypeptide of 116 amino acids, has been reported to be an effective biomarker for bacterial infection [9,10]. A meta-analysis showed that the sensitivity and specificity of PCT for differentiating bacterial from viral infections were 0.92 and 0.86, respectively [11]. The PCT concentration in both serum and CSF of BM patients is increased, and both can serve as diagnostic markers for BM detection [12–15]. However, it is remains unknown whether serum or CSF PCT is better for the diagnosis of BM.

Therefore, the aim of the present study was to compare the diagnostic accuracy between serum and CSF PCT determination in parallel. We focused our investigations on whether serum and CSF PCT had a high diagnostic value for BM among suspected meningitis patients.

2. Material and methods

2.1. Participants

A total of 150 patients with meningitis-like manifestations, who were admitted to the Second People's Hospital of Wuxi or the Changhai

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http://dx.doi.org/10.1016/j.clinbiochem.2015.06.017
0009-9120/

Hospital of Shanghai between January 2011 and December 2013, were prospectively and consecutively enrolled in this study. The inclusion criteria were as follows: 1) patients with two of the following symptoms or signs: fever, confusion, headache, or nuchal rigidity; 2) older than 18 years old; 3) no determination of a meningitis pathogen on admission; and 4) CSF leukocyte count greater than 5×10^6/L [16]. Patients who were infected with bacteria and received antibiotic therapy during the past two weeks were excluded.

The present study was approved by the Ethics Committees of the Second People's Hospital of Wuxi and the Changhai Hospital of Shanghai. Written informed consent was obtained from all patients included in this study.

2.2. PCT test methods

The serum and CSF samples were drawn within 8 h after admission. After completing routine bacterial and chemical analyses (e.g., CSF leukocyte count, protein level determination, and bacterial culture), the serum and CSF samples were stored immediately at −80 °C. In June 2014, all the serum and CSF samples were subjected to PCT concentration determination by immunolumino-metric assay (LUMItest PCT, BRAHMS Diagnostica, Berlin, Germany). The laboratory technicians were blinded to the clinical information of the subjects.

2.3. Diagnosis of BM

Leukocyte count and protein level were determined in the CSF samples from all admitted subjects. In addition, the blood and CSF samples were subjected to bacterial culture and Gram staining. Finally, the CSF samples were tested for viral infection, including CMV, ECHO, and HSV, by quantitative polymerase chain reaction (qPCR) to detect viral infection. Patients with positive CSF bacterial culture or Gram staining, but negative qPCR test, were diagnosed as BM, and antibiotic therapy was initiated immediately. The patients who tested positive for viral infection according to the qPCR test, but had negative CSF bacterial culture and Gram staining, were diagnosed as viral meningitis. For the cases with negative bacterial culture, Gram staining and qPCR, experimental therapy with antibiotics was introduced and the outcomes of the patients were documented [17]. The final diagnosis was made by two experienced physicians using the CSF laboratory findings and treatment response.

2.4. Statistical analysis

For continuous variables, Mann–Whitney U test or Student's t-test was used to assess whether the differences had statistical significance. For categorical variables, χ^2 test was used. Spearman's rank correlation coefficient was employed to analyze the relationship between two continuous variables. All continuous variables were reported as median (interquartile) or mean (SD) values. The diagnostic accuracy of PCT for BM was analyzed by receiver operator characteristic (ROC) curve analysis. The cut-off value for the PCT level was established by seeking the maximum accuracy (the proportion of true positive to true negative results). The areas under ROC curve (AUCs) were compared by the method developed by DeLong et al. [18]. *P* value of 0.05 or less was considered statistically significant. All tests were two-sided, and all statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) and SigmaPlot 11.0 for Windows.

3. Results

3.1. Demographic and clinical characteristics of the subjects

Of the 150 patients who were initially included in this study, 13 were returning patients and 17 had used antibiotics prior to admission. Finally, 120 meningitis patients were eligible for final analysis. All patients were given an initial and a final diagnoses. Of these subjects, 30 who had a positive CSF or blood bacterial culture or Gram staining, but a negative PCR viral infection test, were initially diagnosed as BM. A total of 59 patients were categorized into the non-BM group because of positive PCR finding and negative CSF bacterial culture or Gram staining. For the remaining subjects, antibiotic therapy was initiated and the responses to the therapy were monitored. The final diagnosis was based on the patients' CSF leukocyte count, protein and glucose determination, as well as their responses to antibiotic therapy. Conclusively, 45 subjects were categorized into BM and 75 were categorized into the non-BM group. The clinical characteristics at baseline are shown in Table 1. Among the 75 non-BM patients, 18 were diagnosed as Coxsackie virus-induced meningitis, 17 were infected with the ECHO virus, 14 were infected with the herpes virus, 5 were infected with the EB virus, 3 were infected with the varicella zoster virus, 2 were infected with the paramyxovirus, and 16 were infected with an unknown virus. Among the BM group, 12 were infected with *Streptococcus pneumoniae*, 10 with *Diplococcus intracellularis*, 8 with *Staphylococcus aureus*, and 15 with unknown bacteria.

3.2. Increased serum and CSF PCT levels in the bacterial meningitis patients

As shown in Fig. 1, the median serum concentration of PCT in the BM and non-BM patients was 4.22 ng/mL and 0.41 ng/mL, respectively. In addition, the CSF PCT concentration in the BM and non-BM patients was 1.88 ng/mL and 0.34 ng/mL, respectively. Both the serum and CSF PCT concentrations in the BM patients were significantly higher than those of the non-BM patients ($P < 0.01$ for both).

3.3. Relationship between the CSF and serum PCT levels in the BM and non-BM patients

As shown in Fig. 2, the serum PCT level was positively correlated with the CSF PCT level among all meningitis patients, resulting in a correlation coefficient (R) of 0.64 ($P < 0.01$). We further analyzed the relationship between the serum and CSF PCT levels in the BM and non-BM patients, respectively. A significant positive correlation between the serum and CSF PCT levels ($R = 0.69$, $P < 0.01$) was observed in the BM patients but not in the non-BM patients.

In addition, we also analyzed the relationships between the PCT level and the CSF leukocyte count as well as the CSF protein level. The serum PCT level was positively correlated with the CSF leukocyte count ($R = 0.36$, $P = 0.02$) and with the protein level ($R = 0.39$, $P = 0.01$) in the BM patients but not in the non-BM patients.

3.4. Diagnostic accuracy of the serum and CSF PCT levels for BM patients

Fig. 3 shows the ROC curve of the serum and CSF PCT for the diagnosis of BM. The AUC for serum and CSF PCT was 0.96 (95% CI: 0.93–1.00)

Table 1
Demographic and clinical characteristics of the subjects.

	BM	Non-BM	*P*
Number of patients	45	75	–
Age (years)	50 ± 18	47 ± 19	0.34
Gender (male/female)	30/15	55/20	0.53
Clinical signs or symptoms			
Median period between symptom onset and admission (h)	43 (25, 52)	43 (30, 54)	0.26
Fever (yes/no)	45/0	60/15	<0.01
Headache (yes/no)	45/0	75/0	1.00
Nuchal rigidity (yes/no)	44/1	70/5	0.41
Confusion (yes/no)	2/43	1/74	0.55
CSF laboratory findings			
Leukocyte count (10^6/L)	3800 (620, 7500)	280 (58, 500)	<0.01
Protein (g/L)	0.68 (0.40, 0.94)	0.39 (0.25, 0.56)	<0.01

Note: Values are the median and quartile, where appropriate.

Please cite this article as: Shen H-Y, et al, Direct comparison of the diagnostic accuracy between blood and cerebrospinal fluid procalcitonin levels in patients with meningitis, Clin Biochem (2015), http://dx.doi.org/10.1016/j.clinbiochem.2015.06.017