Serum Procalcitonin Levels in Patients with Acute Central Nervous System Infections

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Abstract

BACKGROUND: Bacterial infections of the brain are associated with high mortality and neurological sequelae, whereas viral diseases are usually self-limiting. A fast and easy-to-perform biomarker is needed to improve management in these patients.

AIM: Procalcitonin (PCT) testing has already been implemented in many laboratories for evaluating septic patients and it is an easily accessible biomarker, so we aimed to examine its role specifically in discriminating acute bacterial from viral infections of the central nervous system (CNS).

MATERIALS AND METHODS: This prospective study included 80 patients with both clinical symptoms and laboratory findings suggesting acute CNS infection. The microbiological analysis included direct microscopy, culturing, latex-agglutination test, and multiplex polymerase chain reaction. PCT levels were measured by enzyme-linked fluorescent assay technology.

RESULTS: Following the results of the microbiological analysis, the cases were divided into three groups – bacterial 26.3% (n = 21), viral 17.5% (n = 14), and unidentified neuroinfections – 56.2% (n = 45). A statistically significant difference in the median serum PCT was observed between the bacterial and viral neuroinfections (p = 0.004) as well as between bacterial and unidentified infections of the brain (p = 0.000). No significant difference was found (p = 1.000) when comparing viral and unidentified neuroinfection. The area under the receiver operating characteristic curve for serum PCT was 0.823 but could be increased to 0.929 when combining serum PCT and C-reactive protein (CRP).

CONCLUSION: Serum PCT levels are significantly higher in patients with acute bacterial infections of the brain. As a stand-alone biomarker, its discriminatory power is not superior to the classical laboratory parameters in the cerebrospinal fluid and serum CRP. However, when combined with serum CRP, excellent discriminatory power is observed.

Introduction

Central nervous system (CNS) infections are medical emergencies having diverse etiology with viruses and bacteria being the most common pathogens [1]. Bacterial infections are associated with high mortality and neurological sequelae, whereas viral diseases are in most cases self-limiting and have a good prognosis [2]. The clinical findings are poor discriminator of the etiology so it could sometimes be difficult to distinguish between bacterial and aseptic meningitis in patients presenting with an acute CNS infection [3]. The gold standard for laboratory evaluation includes cerebrospinal fluid (CSF) analysis of cell count, glucose, and protein levels along with serum C-reactive protein (CRP) [4]. There are many recommendations to initiate antibiotic therapy as soon as possible until culture results are available within the next 24–78 h, giving the fact that the mortality rate is increasing with any delay of antibiotic administration if a bacterial infection of the brain is present [5], [6]. For these various reasons, a fast and easy-to-perform biomarker test is needed to improve the management of such patients, aiding the decision about the start of the antibiotic treatment. Giving the heterogeneous results reported in various scientific researches, the validation of this biomarker in the management of patients with acute neuroinfections is still challenging. Because procalcitonin (PCT) testing has already been implemented in many laboratories for evaluating septic patients and it is an easily accessible biomarker, we aimed to examine its role specifically in discriminating acute bacterial from viral infections of the CNS.

Materials and Methods

This prospective study included 80 patients with both clinical symptoms and laboratory findings of an...
acute CNS infection, admitted to “St. George” University Hospital – Plovdiv. Patients presented with fever, signs of meningeal irritation, altered consciousness, and abnormal CSF – pleocytosis, elevated protein, and decreased or normal glucose levels. A paired sample of serum and CSF was collected through lumbar puncture and venipuncture, using an aseptic technique.

Following the algorithm, the CSF analysis included cell count, protein, and glucose levels, as well as microbiological examination to determine the etiology. CRP and PCT levels were detected in the patient’s sera. PCT levels were measured by enzyme-linked fluorescent assay technology (Vidas, BioMerieux). Values below the detection threshold of 0.05 ng/ml were considered as zeroes. Serum CRP levels were examined by an immunoturbidimetric method applied on a Beckman Coulter AU analyzer (System). Routine methods such as direct microscopy and culturing were used for microbiological analysis. CSF samples were also subject to slide-agglutination test (Pastorex, Biorad) and genetic analysis by multiplex polymerase chain reaction (PCR) (FilmArray, BioMerieux). Microscope slides stained by Gram, methylene blue, and Ziehl-Neelsen were observed using immersion oil light microscopy. Samples were cultured on a blood agar plate and Levinthal’s medium incubated for 48 h at 36 ± 1°C with 5–10% of CO₂ enriched atmosphere. Another set of the blood agar plate and Levinthal’s medium was incubated at 36 ± 1°C without further CO₂ supplementation along with eosin-methylene blue agar for Gram-negative bacteria. Sabouraud-dextrose agar for fungi was also inoculated and kept up to 14 days.

Numeric variables are presented as median (25th percentile and 75th percentile) due to the lack of normal distribution. Categorical variables are presented as a percentage (%). Kruskal-Wallis H test was applied to compare the ranked median between more than two independent groups. Logistic regression was used to generate a receiver operating characteristic (ROC) curve as an assessment of the discriminatory power of each parameter in the diagnosis of bacterial neuroinfections. A general scale for interpreting area under the curve (AUC) values classifies an AUC value of 0.90–0.99 as excellent discrimination, a value of 0.80–0.89 as good discrimination, a value of 0.70–0.79 as fair discrimination, and a value of 0.51–0.69 as poor discrimination. Best cutoff values were chosen using Youden’s index (highest sensitivity + specificity − 1). A two-sided p < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics v. 26 software (IBM Corp., Chicago, IL, USA).

This study was in accordance with the Bulgarian laws and the Standards for good medical practice. No patients were admitted or were subject to lumbar puncture and/or venipuncture, only for the purpose of the presented study.

Results

The basic demographic characteristics of the 80 studied patients are presented in Table 1. Following the results of the microbiological analysis, the cases were divided into three groups based on the etiology – bacterial neuroinfection (BN), viral neuroinfection (VN), and unidentified neuroinfection (UN). Bacterial CNS infection was found in 26.3% (n = 21), whereas viruses were detected in 17.5% (n = 14) of the patients. In the majority of the cases (56.2%; n = 45), the etiology of the disease remained unidentified. *Streptococcus pneumoniae* was the predominant pathogen among bacteria in 57.1% (n = 12) of the patients, followed by *Staphylococcus aureus* – 14.3% (n = 3), *Listeria monocytogenes* – 9.5% (n=2), *Haemophilus influenzae* – 9.5% (n = 2), *Neisseria meningitidis* – 4.8% (n = 1), and *Escherichia coli* – 4.8% (n = 1).

![Figure 1](https://www.id-press.eu/mjms/index)

Table 1: Basic demographic characteristics of the studied patients

| Parameter | BN (n = 21) | VN (n = 14) | UN (n = 45) |
|-----------|------------|------------|------------|
| Age in years, median (range) | 59 (1–88) | 4.5 (0.6–60) | 27 (0.08–77) |
| Males, n (%) | 14 (66.7) | 6 (42.9) | 23 (51.1) |
| Females, n (%) | 7 (33.3) | 8 (57.1) | 22 (44.9) |

1-BN: Bacterial neuroinfection; 2-VN: Viral neuroinfection; 3-UN: Unidentified neuroinfection.

Enteroviruses were the leading cause of VN – 42.9% (n = 6). We also detected HHV 6 – 21.4% (n = 3), HSV-1 – 14.3% (n=2), VZV – 14.3% (n = 2), and HSV-2 – 7.1% (n = 1).

Our data indicate that all the studied parameters in the CSF compartment (cells, glucose, and protein levels), as well as serum CRP and PCT levels, significantly differ across the observed groups. The results are presented in Table 2. The distribution of serum PCT was not the same across the studied groups (W = 28.10; p = 0.000). A statistically significant difference in the median PCT was observed between the BN and VN (W = 22.55; p = 0.004) as well as the BN and VN (W = 22.55; p = 0.004) as well as VN and UN (W = 22.55; p = 0.004). We did not find a significantly different median value between VN and UN (W = 22.55; p = 1.000) – Figure 1.
### Table 2: Medians of the studied parameters

| Parameter                      | Parameter  | Median (25th – 75th percentile) |
|--------------------------------|------------|----------------------------------|
| CSF white blood cell count     | BN (m=21)  | 426 (136–2560)                   |
| CSF protein                    | VN (n=14)  | 20.5 (2.75–64.75)                |
| CSF glucose                    | UN (n=32)  | 12 (3–100.5)                     |
| CSF/glucose ratio              | W (p-value)| 26.54 (0.000)                    |
| Serum CRP (mg/l)               |            | 0.11 (0.00–0.84)                 |
| Serum PCT (ng/ml)              |            | 0.63 (0.46–0.78)                 |
| Serum CRP + CSF WBC            |            | 3.92 (3.71–4.75)                 |
| Serum CRP + CSF Protein        |            | 237 (135–308)                    |

1-BN: Bacterial neuroinfection; 2-VN: Viral neuroinfection; 3-UN: Unidentified neuroinfection; 4-Kruskal-Wallis H test value; 5-CSF: Cerebrospinal fluid; 6-white blood cell count; 7-CRP: C-reactive protein; 8-PCT: Procalcitonin; Data are presented as median (25th – 75th percentile).

When combining PCT with other parameters, the AUC is slightly increased, with the largest area observed when combining serum PCT and serum CRP. The corresponding ROC curves are shown in Figure 2.

By measuring the AUC, we found excellent discriminatory power (AUC >0.9) for CSF protein content, glucose level, CSF/glucose ratio, and serum CRP. The AUC for CSF WBC count and serum PCT was 0.859 and 0.823, respectively. All the results were statistically significant. Data are presented in Table 3.

### Table 3: Estimated AUC for the studied parameters and combination of parameters

| Parameter                      | AUC          | SE           | p-value       | 95% CI       |
|--------------------------------|--------------|--------------|---------------|--------------|
| CSF WBC                        | 0.859        | 0.072        | 0.001         | 0.718–1.000  |
| CSF protein                    | 0.905        | 0.033        | 0.000         | 0.900–1.000  |
| CSF glucose                    | 0.901        | 0.058        | 0.000         | 0.788–1.000  |
| CSF/glucose ratio              | 0.922        | 0.052        | 0.000         | 0.820–1.000  |
| Serum CRP                      | 0.939        | 0.051        | 0.000         | 0.840–1.000  |
| Serum PCT                      | 0.923        | 0.091        | 0.000         | 0.645–1.000  |
| Serum PCT + CSF WBC            | 0.869        | 0.096        | 0.000         | 0.733–1.000  |
| Serum PCT + CSF Protein        | 0.914        | 0.082        | 0.000         | 0.754–1.000  |
| Serum PCT + CSF WBC            | 0.888        | 0.084        | 0.000         | 0.724–1.000  |
| Serum PCT + CSF Protein        | 0.920        | 0.077        | 0.000         | 0.769–1.000  |
| Serum PCT + Serum CRP          | 0.929        | 0.053        | 0.000         | 0.826–1.000  |

AUC: Area under the curve; 1-ROC: Receiver operating characteristic curve; 2-SE: Standard error; 3: Significance level; 4: Confidence Interval; 5-CSF: Cerebrospinal fluid; 6-WBC: White blood cell count; 7-CRP: C-reactive protein; 8-PCT: Procalcitonin.

**Discussion**

PCT is a precursor protein produced mainly by the C-cells of the thyroid gland that is further cleaved into calcitonin, which is involved in calcium homeostasis. Bacterial pathogens can upregulate the CALC-1 gene expression by their antigens or indirectly by inducing the production of interleukin 6 (IL-6) and IL-1 [7]. In addition, many different extra-thyroid tissues can also produce this protein when stimulated by bacterial antigens or the cytokines secreted after macrophage activation. These lack the ability to cleave the PCT into calcitonin, thus leading to a rapid increase in PCT levels in the serum [7], [8]. Pure viral infections do not lead to a sufficient increase in PCT levels due to a decrease in tumor necrosis factor-α, which is essential for its production and viral interferons-γ suppresses the PCT expression [8], [9]. Local bacterial colonization or infection does not cause an increase above the detection limit but is secreted into circulation during severe systemic bacterial infection [10]. Described back in 1993 as a marker of sepsis; nowadays, this molecule is included in different antibiotic stewardship algorithms for initiation and discontinuation of antimicrobial therapy, aiming to reduce the excessive antibiotic consumption [11], [12], [13]. PCT production could also be initiated by various non-infectious causes such as autoimmune disorders, after liver transplantation, rhabdomyolysis, and heat shock [10]. Lower respiratory tract diseases and pleural diseases can also be associated with an increase in serum PCT [10], [14], [15]. Following the first publication on PCT measurement in patients with meningitis and bacterial meningitis in 1997, numerous studies are still evaluating the role of this biomarker for differentiation of bacterial from viral infections but unfortunately with diverse results [16].

Schwarz et al. also reported the same tendency we observed in our study, that the serum PCT and CRP, WBC count, protein, and glucose content are significantly higher in those with BN when compared to non-bacterial infection of the brain [17]. We similarly conclude that the glucose ratio significantly differs between these groups, which are in contrast to the cited research.

The reported median value of serum PCT by Jereb et al. in the patients with bacterial CNS infections was higher (6.45 ng/ml; 0.25–43.76 ng/ml) than the median, we observed for these patients – 2.47 ng/ml; 0.05–17.06 ng/ml [18]. Similarly, the team reported a higher median in the group of VN (0.27 ng/ml; 0.05–0.44 ng/ml) when compared to our results (0.11 ng/ml; 0.05–0.84 ng/ml).

A systematic review by Wei et al. on PCTs role in patients with acute bacterial meningitis concluded that both serum and CSF PCT levels were effective in differentiating patients with acute bacterial meningitis,
with the serum PCT having superior diagnostic potential when compared to the CSF. Even more, the serum PCT alone was a sufficient biomarker to indicate or rule out bacterial meningitis but not so for the CSF PCT [19]. The extensive use of microbiological methods to identify the causative agent in our study resulted in not having a sufficient volume of the CSF specimens to be tested for PCT.

According to the study on 50 patients with meningitis, the serum CRP AUC (0.889) was greater than the serum PCT AUC (0.608) [20]. Although the reported AUC of serum PCT in our study is larger (0.823), we also found that serum CRP is superior to serum PCT in a patient with acute infection of the CNS. The reported by the team best cutoff value of serum PCT is 0.6 ng/ml. On the other hand, a different study concludes that CRP is inferior to serum PCT and CSF protein content [21]. Alkholi et al. concluded in their paper that serum PCT has a better diagnostic in comparison with CRP and leukocyte count. Our data suggest that serum PCT is neither superior to CRP or WBC count [22].

The best cutoff level of serum PCT that we determined is 0.25 ng/ml (sensitivity 83.3% and specificity 72.7%). Although we calculated lower sensitivity and specificity at this particular cutoff, the value is quite similar to some other studies. Viallon et al. published in two separate papers, reported the best cutoff of 0.20 ng/ml (sensitivity of 95, and a specificity of 100%), and 0.28 ng/ml (sensitivity 95% and specificity 100%), respectively [21], [23].

When combining PCT with other parameters, the AUC is slightly increased. The best increase of the AUC is observed when matching serum PCT and serum CRP. According to a study by Markéta et al., this combination offers the best sensitivity and specificity, regardless of focusing on the fungal infection [24]. The team reported that the combination of high CRP with low PCT could be suggestive for fungal infections in immunocompromised hosts of the brain. We assume that the high serum PCT and CRP levels could be pointing toward a BN.

In the patient who experienced E. coli K1 meningitis, we determined relatively low serum PCT levels for bacterial infection – 0.08 ng/ml. The patient did not receive any antibiotics before the lumbar puncture and was tested positive for the bacterium on the direct microscopy, culturing, latex-agglutination test, and multiplex PCR. Contamination of the sample could be excluded due to the clinical picture, the severe onset, and the abnormal CSF parameters, suggesting BN. Given the fact that, ventriculoperitoneal shunt was placed before the onset of infection, the final diagnosis of shunt-associated neuroinfection was established. The bacterium had never appeared in the blood, which was confirmed by several negative blood cultures, but introduced directly into the CNS through the shunt. These findings could explain the relatively low serum PCT, which seems to be quite sensitive to the presence of bacterial pathogens in the bloodstream itself. Although the hematogenous spread is the most common mechanism of invasion to the CNS, it is reasonable to assume that if a particular bacterium is not found in the blood before reaching the CNS, lower serum PCT might be observed, thus limiting the application of this biomarker in such patients.

On the other hand, an HSV-1 PCR-positive patient had serum PCT levels of 44.39 ng/ml. We were not able to recover any bacteria. This could be probably explained to some extent by the acute necrotizing encephalopathy observed in the patient, not only confirming the etiology but also pointing to other mechanisms, like necrosis, that might lead to an increase in PCT in the serum.

**Study limitations**

However, some limitations should be noted. First, a limitation of our study is the relatively small number of patients in the groups we compare. Several methods were used simultaneously for microbiological diagnosis to increase the detection rate and recognize the etiology of the neuroinfection. Unfortunately, the majority of the cases remained unidentified, although the findings were consistent with a viral or bacterial infection of the CNS. Second, specimen collection was not standardized with respect to the onset of the disease. They were obtained as soon as possible when patients were presenting with symptoms but the actual time from one patient to another may vary, thus not evaluating the effect of the serum PCT’s kinetic properties, which might influence the discriminatory power of the biomarker.

**Conclusion**

In summary, serum PCT levels are significantly higher in patients with acute bacterial infections of the brain and could differentiate between bacterial and non-BNs. We conclude that as a stand-alone biomarker, its discriminatory power is not superior to the classical laboratory parameters in the CSF and serum CRP. The best cutoff value of serum PCT that we calculated is 0.25 ng/ml (sensitivity = 83.3% and specificity = 72.7%). The PCT’s discriminatory potential can be best increased when combining with serum CRP.

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