Predictive Value of Serum and Cerebrospinal Fluid Procalcitonin Levels for the Diagnosis of Bacterial Meningitis

M. Jereb, I. Muzlovic, S. Hojker, F. Strle

Abstract

Background: The value of serum and cerebrospinal fluid (CSF) procalcitonin for differentiating between acute bacterial and viral meningitis was assessed and compared to other parameters which are usually used in clinical practice.
Patients: 45 adult patients (20 with bacterial and 25 with tick-borne encephalitis, TBE) were included in this prospective study.
Results: The median serum procalcitonin level in patients with bacterial meningitis was 6.45 ng/ml (range 0.25–43.76 ng/ml) and in the group with viral meningitis 0.27 ng/ml (range 0.05–0.44 ng/ml). 11 patients with bacterial meningitis had an elevated procalcitonin concentration not only in serum, but also in CSF. A serum procalcitonin level > 0.5 ng/ml had a positive predictive value for bacterial meningitis of 100% and a negative predictive value of 93%, while corresponding values for CSF procalcitonin were 100% and 74%, respectively.
Conclusion: Serum and CSF procalcitonin concentrations > 0.5 ng/ml appear to be a reliable indicator of bacterial central nervous system (CNS) infection, with maximal positive predictive values and high negative predictive values.

Key Words

Procalcitonin · Meningitis · Serum · Cerebrospinal fluid · Predictive value

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Introduction

Despite advances in antibiotic therapy, acute bacterial meningitis continues to be a significant cause of morbidity and mortality. Rapid diagnosis and appropriate treatment have a crucial influence on survival [1]. The examination of CSF is a cornerstone in the diagnostic procedure for patients with suspected meningitis. A CSF : serum glucose ratio < 0.23, a CSF protein concentration > 2.2 g/l and > $1{,}180 \times 10^6$/l neutrophils have been accepted as individual parameters indicating bacterial meningitis with a high degree of probability [2]. With a Gram stain examination of CSF and CSF culture, the causative agent is found in 60–90% of purulent meningitis cases [3]. Because culture results are not available immediately, treatment decisions are, as a rule, based on other CSF findings. However, routine blood and CSF information occasionally fails to differentiate between acute bacterial and acute viral meningitis. Patients with viral meningitis could have clinical and laboratory parameters indicating bacterial infection, which usually leads to unnecessary antibiotic therapy. On the other hand, a delay in antimicrobial treatment could be fatal in a case of uncharacteristic bacterial meningitis [4].

During the last few years, there have been several studies on the new inflammation peptide, procalcitonin (PCT). Its serum concentration increases in a setting of systemic bacterial infection, while patients with viral infections have normal or only slightly increased PCT serum levels [5, 6]. There have been only a few reports in the literature on serum PCT as a marker of bacterial meningitis. *Gendrel* et al. [7] reported that measurement of the plasma PCT level might be of value in differentiating between bacterial and viral meningitis in children. Similar conclusions were made by *Viallon* et al. [8] and *Schwarz* et al. [9], who found elevated serum PCT levels during bacterial meningitis in adults.

The present study was performed to evaluate the predictive value of elevated serum and cerebrospinal fluid PCT concentrations for the diagnosis of acute bacterial meningitis and to compare them with the standard laboratory markers of bacterial infections, such as serum C-reactive protein (CRP) level, total leukocyte count and percentage of immature polymorphonuclear cells (PMN) in serum, total leukocyte and PMN count in CSF, CSF protein concentration and CSF:serum glucose ratio.

Patients and Methods

The study protocol was approved by the Ethics' Committee of the Ministry of Health of the Republic of Slovenia.

20 consecutive adult patients with acute bacterial meningitis and 25 consecutive patients with tick-borne encephalitis (TBE),

M. Jereb *(corresponding author)*, **I. Muzlovic, S. Hojker, F. Strle**
University Medical Centre Ljubljana, Japljeva 2, 1525 Ljubljana, Slovenia;
Phone: (+386/1) 2310558, Fax: -2302781, e-mail; matjaz.jereb@kclj.si

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admitted in 1998 to the Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia, were included in this prospective study. Detailed patients' characteristics, including Glasgow Coma Scale (GCS) and acute physiology and chronic health evaluation (APACHE) III score were recorded on admission.

From all patients included in the study, blood samples were drawn and a lumbar puncture performed immediately after admission to hospital when meningitis was clinically suspected, i.e. prior to the eventual antibiotic treatment. Biochemical and cytological examinations of CSF samples were performed, including the measurement of leukocyte counts, glucose level and protein concentration. In blood samples collected at the same time, serum CRP level, leukocyte count and glucose concentration were measured. Routine laboratory methods were used. In addition, blood and CSF PCT levels were determined on admission using an immunoluminometric assay adapted from the immunoradiometric assay (LUMItest PCT, now supplied by BRAHMS Diagnostica, Berlin, Germany). PCT values were not followed during the hospitalization. If samples were not analyzed within 4 h after blood or CSF had been taken, they were stored at –20 °C. The detection limit of this test is 0.1 ng/ml. Interassay and intra-assay variations at both low (0.01 ng/ml) and high (500 ng/ml) concentrations were less than 8% and 7%, respectively. With this assay, serum levels of PCT in healthy adults < 0.1 ng/ml and values > 0.5 ng/ml are considered to be abnormally elevated [6, 10].

The essential criterion for the diagnosis of meningitis was the presence of an elevated CSF leukocyte count ($> 5 \times 10^6$/l) in a patient with the appropriate clinical features [11]. Meningitis was defined to be bacterial by the finding of a positive CSF Gram-stained smear or by the isolation of an appropriate bacterium from CSF and/or blood. Patients with aseptic meningitis and positive serum TBE IgM and/or a 4-fold rise of specific IgG antibodies were interpreted as having TBE [12]. According to these criteria, patients were divided into a group with bacterial meningitis and a group with viral meningitis (TBE).

A comparison of the group with bacterial meningitis and the group with viral meningitis (TBE) was made with the nonparametric Mann-Whitney test for continuous variables and by the Chi-square test for gender. For several laboratory parameters, sensitivity, specificity and predictive values were calculated according to standard formulas. A CSF : blood glucose ratio < 0.23, a CSF protein concentration > 2.2 g/l, a CSF leukocyte count > 2,000 $\times 10^6$/l, a CSF PMN count > 1,180 $\times 10^6$/l, a blood white cell count $> 10 \times 10^9$/l or at least 15% of immature PMN, a CRP blood level > 50 mg/l and a CSF or serum PCT level > 0.5 ng/ml were assessed as individual parameters indicating bacterial meningitis.

Results

All 25 patients in the viral meningitis group had positive serum TBE IgM antibodies on admission as well as specific IgG antibodies. 16 patients had typical history of a tick bite with a biphasic febrile illness, seven had a biphasic course of illness and no tick bite in the previous few months and in two cases the course of illness was monophasic without data about tick bites. None had a history of symptoms and signs of meningitis during the previous year and none had received TBE vaccination. In all patients in the viral meningitis group specific IgM and IgG antibodies (serum and CSF) to *Borrelia burgdorferi* were negative.

The microorganisms identified in CSF samples of 20 patients with bacterial meningitis consisted of *Streptococcus pneumoniae* (n = 9), *Staphylococcus aureus* (n = 4), *Listeria monocytogenes* (n = 2), *Neisseria meningitidis* (n = 2), *Haemophilus influenzae* b (n = 1) and *Clostridium perfringens* (n = 1). Identical microorganisms were also identified in blood cultures in ten patients. In one case CSF and blood cultures were negative but a positive Gram smear (gram-positive cocci) of purulent CSF attested to bacterial meningitis.

The patients' characteristics, as well as blood and CSF findings for bacterial and viral meningitis cases, are presented and compared in table 1. Highly significant differences between bacterial and viral group were found for the GCS, APACHE III score and for all laboratory parameters determined in this study. However, comparing patients with bacterial and patients with viral meningitis, all these elements had a wide distribution range, often with a large area of overlap. There was no correlation between disease severity on admission and serum PCT value according to GCS and APACHE score.

Table 1
Patients' characteristics and blood and CSF findings in cases of bacterial and viral meningitis.

	Bacterial meningitis n = 20 Median (range)	TBE n = 25 Median (range)	P-value
Age (years)	55 (16–77)	49 (22–66)	0.282
Gender (M/F)	11/9	13/12	0.920
GCS	11.5 (3–15)	15 (7–15)	< 0.001
APACHE III	51.5 (3–86)	11 (2–39)	< 0.001
Serum leukocyte count (10^9/l)[a]	19.2 (4.4–30.0)	10.0 (5.0–17.8)	< 0.001
Serum immature PMN (%)[b]	12 (1–36)	1 (0-15)	< 0.001
CRP in serum (mg/l)[c]	152.5 (25–367)	8 (3–78)	< 0.001
CSF leukocyte count (10^6/l)[d]	1,368 (38–31,467)	123 (13–448)	< 0.001
CSF PMN (10^6/l)[e]	1,133 (25–30,187)	21 (2–267)	< 0.001
CSF protein (g/l)[f]	6.8 (0.91–17.44)	0.73 (0.4–2.3)	< 0.001
CSF : blood glucose ratio[g]	0.09 (0.01–0.53)	0.55 (0.35–0.89)	< 0.001
PCT in serum (ng/ml)	6.45 (0.25–43.76)	0.27 (0.05–0.44)	< 0.001
PCT in CSF (ng/ml)	1.27 (0.13–2.75)	0.28 (0.08–0.43)	< 0.001

TBE: tick-borne encephalitis; GCS: Glasgow Coma Scale; APACHE: acute physiology and chronic health evaluation; CRP: C-reactive protein; CSF: cerebrospinal fluid; PMN: polymorphonuclear cell; PCT: procalcitonin

Normal reference laboratory values and methods: [a] serum leukocyte count 4.0–10.0 $\times 10^9$/l by automated cell counter; [b] serum immature PMN 0–5% by manual count; [c] CRP in serum 0–12 mg/l by nephelometry; [d] CSF leukocyte count 0–5 $\times 10^6$/l by manual count; [e] CSF PMN 0 by manual count; [f] CSF protein 0.15–0.45 g/l by turbidometry; [g] CSF : blood glucose ratio > 0.5 by calculation

Thus, in patients with bacterial meningitis, three had a serum leukocyte count in the normal range, 11 had less than 15% of immature PMN in peripheral blood, two had a CRP concentration < 50 mg/l, 13 had a CSF leukocyte count $< 2{,}000 \times 10^6$/l and 11 had a CSF PMN count $< 1{,}180 \times 10^6$/l, six had a CSF protein concentration < 2.2 g/l and three had a CSF : serum glucose ratio in the normal range.

In the group of patients with TBE, 13 had a leukocyte count in serum $> 10 \times 10^9$/l, one had 15% of immature PMN in peripheral blood, two had a CRP level > 50 mg/l and one had a CSF protein concentration > 2.2 g/l.

The median serum PCT level in patients with bacterial meningitis was 6.45 ng/ml (range 0.25–43.76 ng/ml). Two patients had a PCT concentration in serum below the cutoff value 0.5 ng/ml, and in both cases *L. monocytogenes* was identified in CSF. 11 out of 20 (55%) patients with bacterial meningitis had a CSF PCT level > 0.5 ng/ml, and in all of them the PCT concentration was also elevated in serum. The median PCT level in CSF was 1.27 ng/ml (range 0.13–2.75 ng/ml) and was in all cases below the serum level. Patients with a PCT concentration in CSF > 0.5 ng/ml had a higher serum PCT level on average compared to patients with a CSF PCT levels < 0.5 ng/ml; however, the difference was not statistically significant ($p = 0.089$).

The median serum PCT level in patients with viral meningitis was 0.27 ng/ml (range 0.05–0.44 ng/ml) and the median CSF level was 0.28 ng/ml (range 0.08–0.43 ng/ml).

The sensitivity, specificity and predictive values of several laboratory parameters, including serum and CSF PCT levels for the diagnosis of acute bacterial meningitis, are shown in table 2.

Discussion

The diagnosis of bacterial meningitis has been based on the cytobiochemical characteristics of CSF samples and on positive CSF culture. Unfortunately, CSF culture results are not available early in the course of a diagnostic procedure or may even remain negative, and no single value of any CSF or blood parameter is absolutely discriminatory between bacterial and viral meningitis [1–4]. Overlapping results were found also in our study for all the parameters examined.

In order to assess the potential value of PCT to predict bacterial meningitis, serum and CSF samples were collected and PCT levels were determined on admission, prior to the institution of antimicrobial therapy. Elevated PCT concentrations were found exclusively in patients with bacterial meningitis. Thus, our results corroborate previous findings demonstrating the association of elevated PCT with bacterial, not viral meningitis [7–9]. However, in the present study, two (10%) patients with bacterial meningitis had a serum PCT level below a cutoff value of 0.5 ng/ml. In both cases *L. monocytogenes* was identified in CSF. *Viallon* et al. [8] also found low serum PCT levels in two out of 23 (8.7%) patients with bacterial meningitis, but both had received previous antibiotic therapy, while our patients had not. *Schwarz* et al. [9] found PCT levels in normal limits in five patients with bacterial meningitis. However, when we looked at the bacteria isolated, their data are not comparable with our results. On the other hand, *Gendrel* et al. [7], who measured the plasma PCT level in 59 children with bacterial or viral meningitis, found serum PCT level above 4.8 ng/ml in all 18 patients with bacterial infection, including a patient from whom *L. monocytogenes* was isolated in CSF.

The mechanisms responsible for the marked increase of serum PCT during systemic bacterial infections and the exact site of its production remain enigmatic [13–15]. In healthy volunteers PCT induction was stimulated by the intravenous application of bacterial endotoxin. PCT values increased a few hours after the increase of IL-6 and TNF-α, suggesting that the stimulation of PCT is closely related to the induction of proinflammatory cytokines [16]. In meningitis, as well as in other infections, the proinflammatory effect of cytokines is controlled by anti-inflammatory cytokines. Anti-inflammatory cytokines, while potentially beneficial, may in certain situations impair the host's inflammatory response [17]. Several factors, including the variability in bacterial species and age of a patient, may influ-

Table 2
Sensitivity, specificity and predictive values of several laboratory parameters in the diagnosis of bacterial meningitis.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Serum leukocyte count	85	48	56	80
Serum immature PMN	45	96	90	69
CRP serum level	90	92	90	92
CSF leukocyte count	35	100	100	66
CSF PMN	45	100	100	69
CSF : blood glucose ratio	85	100	100	89
CSF protein concentration	70	96	93	80
PCT serum concentration	90	100	100	93
PCT CSF concentration	55	100	100	74

Cutoff values: 10×10^9/l for serum leukocyte count; 15% for immature leukocytes in peripheral blood; 50 mg/l for serum CRP concentration; $2{,}000 \times 10^6$/l for CSF leukocyte count; 1,180 for CSF PMN leukocytes; 0.23 for CSF : blood glucose ratio; 2.2 g/l for CSF protein concentration; 0.5 ng/ml for serum PCT and CSF PCT level
CRP: C-reactive protein; CSF: cerebrospinal fluid; PMN: polymorphonuclear cell; PCT: procalcitonin

ence the proinflammatory and anti-inflammatory cytokines differently, which may result in different serum PCT levels.

Data on the concentration of PCT in CSF are limited. In the study reported by *Gendrel* et al. [7] on the CSF findings of children with bacterial meningitis, PCT was not detected. Similar results were presented by *Viallon* et al [8]. In their study, only two patients with bacterial meningitis (both with a high level of serum PCT) demonstrated an elevated PCT level in CSF; this elevated concentration was attributed to bleeding following a traumatic lumbar puncture. In the present study we found a CSF PCT level > 0.5 ng/ml in 11 patients with bacterial meningitis, and in all of them lumbar puncture was accomplished without macroscopic bleeding in association with a procedure. None had a recent history of head trauma or neurosurgery. All these patients had an elevated PCT concentration in serum, and in all of them it was well above their CSF PCT level. Blood proteins are largely excluded from CSF by the blood/CSF barrier. Under normal conditions proteins enter the CSF by active transport across the capillary endothelium [18]. In the case of CNS infections, elevated CSF protein concentrations usually result from the diffusion of blood proteins as a consequence of the disruption of tight junctions between the endothelial cells of venules and other small meningeal vessels. This mechanism might also have been the reason for the passage of PCT from blood to CSF and for the elevated CSF concentration found in our study.

Another mechanism for the elevated CSF PCT concentrations in patients with meningitis could have been a cytokine-induced PCT secretion from cerebral vascular endothelial cells or from leukocytes. The exact site of PCT production is unknown, but the PCT producing cells seem unable to process this precursor form into the mature hormone calcitonin. Some authors have found PCT-like activity in human leukocytes, others suggest the lungs or the neuroendocrine cells as possible sites of synthesis [13–15]. Several cytokines are present in CSF during meningitis, where they induce endothelial-derived adhesion molecules on the cerebral blood vessels. The activation of cerebral vascular endothelial cells leads to an increase in the CSF leukocyte count [17]. In the present study, CSF PCT concentrations above the serum level were found in nine patients with TBE virus infection. However, the concentrations of PCT were low and the differences were small (statistically not significant), but might suggest direct intrathecal PCT secretion from as yet unknown cells. Therefore, further studies are necessary to determine the origin, metabolic pathways and mediators responsible for the increase in serum and CSF PCT during (bacterial) meningitis.

In conclusion, this study found serum and CSF PCT levels to be reliable markers of bacterial meningitis. A PCT level > 0.5 ng/ml predicts bacterial infection of the CNS better than an elevated serum leukocyte count, percentage of immature PMN leukocytes in peripheral blood, serum CRP and CSF protein concentration. The positive predictive values of serum and CSF PCT were 100%, and were as good as those of classic parameters such as the CSF leukocyte count, the total CSF PMN count and CSF:blood glucose ratio, while the negative predictive value of serum PCT was even higher than those found for other parameters routinely used in clinical practice.

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