Diagnostic utility of serum procalcitonin measurement in bacterial meningitis

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Abstract

Aims: The aim of this study was to assess the role of serum procalcitonin level in the diagnosis of bacterial meningitis and compare it against other laboratory parameters which are used in the clinical practice.

Methods: This cross-sectional study included 32 patients with bacterial and non-bacterial meningitis hospitalized at the Infectious Diseases Service of the University Hospital Center "Mother Teresa" in Tirana, Albania, during April 2010-April 2012. Bacterial meningitis was diagnosed or ruled-out using clinical history, physical examination, cerebrospinal fluid (CSF) laboratory findings, and identification of bacterial agents in CSF, gram staining and cultures. The non-parametric Mann-Whitney test was used to assess between-groups' differences.

Results: The median serum procalcitonin level was higher in patients with bacterial meningitis 22.47 ng/ml (range 2.5-100 ng/ml), while in the group with non-bacterial meningitis it was 0.83 ng/ml (range 0.25-1.46 ng/ml).

Conclusions: Procalcitonin appears to be a more reliable biomarker of bacterial meningitis diagnosis than CRP. A concentration of PCT >2 ng/ml had 100% sensitivity for bacterial meningitis.

Introduction

Acute bacterial meningitis continues to be a significant course of morbidity and mortality, despite advances in antibiotic therapy. Early diagnosis and starting immediate empirical therapy are the key factors to reduce the morbidity and mortality related to bacterial meningitis (1).

Therefore, distinguishing bacterial and aseptic meningitis in the emergency department could help to limit unnecessary antibiotic use and hospital admissions. Because the consequence of delayed diagnosis of bacterial meningitis can be severe, any proposed diagnostic parameter must achieve near 100 % sensitivity. Clinical criteria, gram staining, and bacterial antigen testing of cerebrospinal fluid (CSF) as well as the classic biological markers in the blood (c- reactive protein, white blood cells) or CSF (protein

level, glucose level, white blood cell (WBC) count and neutrophil count), do not offer near 100 % sensitivity with high specificity for distinguishing bacterial meningitis from non-bacterial meningitis (2).

To identify bacterial growth in CSF cultures need at least 2 days, whereas this period is 3-8 days for viral cultures. Lately, intensive research has been carried out to find new and rapid diagnostic parameters for differential diagnosis of bacterial and viral meningitis.

In this condition, a new marker, procalcitonin (PCT) which is a calcitonin propeptide, is supposed to be synthesized in C-cells of the thyroid gland in normal conditions and secreted from leukocytes on the peripheral blood in bacterial infections .The secretion of PCT was found to increase in the presence of bacterial lypopolisaccharides and cytokines. PCT production during inflammation depend from bacterial endotoxins and inflammatory cytokines, interleukins 6 (IL-6) and tumor necrosis factor (TNF alpha) (3,4).

The aim of our study was to assess the role of PCT in diagnosis of bacterial meningitis, and compare PCT with other laboratory standard markers: CRP (C–reactive protein), total leukocyte count, WBC and percentage of polimorphonuclears in CSF and peripheral blood, protein concentration in CSF and the ratio glucose CSF/ glucose serum.

Methods

This study included 32 patients hospitalized at the Infectious Diseases Service of the University Hospital Center "Mother Teresa" in Tirana, Albania, during a two-year period: April 2010 to April 2012. Clinical characteristics of patients were recorded upon admission. Meningitis was diagnosed according to clinical history, physical examination, CSF laboratory findings, identification of bacterial agents in CSF, gram staining and cultures.

Patients enrolled into the study were categorized in two groups:

- G 1-Bacterial meningitis (BM) including 20 patients (12 males and 8 females);
- G 2-Non-bacterial meningitis (NBM) including 12 patients (7 females and 5 males).

Meningitis was defined as bacterial if the CSF findings indicated an increased protein of >2 g/ l, decreased glucose ratio <0.4, leukocytes count >1500x10^6/ l and polymorphonuclear leukocytes domination, identification of bacterial agents in Gram staining and/ or bacterial positive cultures.

Meningitis was defined as non-bacterial meningitis if no bacteria were documented on gram stain or in bacterial culture of CSF, lymphocyte predominance of CSF cells, reduced protein level and increased glucose ratio >0.5 (5,6).

Patients exhibiting another site of infection in addition to meningitis, or who had received prior antibiotic treatment for more than two consecutive days were excluded from the study.

All patients underwent a full clinical examination and the following tests: complete blood count, C-reactive protein, serum procalcitonin and cytochemical study and bacterial culture of CSF.

Blood samples for procalcitonin were taken at the time of admission and after 72 hours, from the waste of blood taken for routine examination.

Complete blood count as part of routine laboratory test was performed by CELL-DYNE 1800 ABBOTT SYSTEM.

Serum procalcitonin was measured by electrochemiluminiscente immunoassay in COBAS INTEGRA 6000 with ELECSYS BRAHMS PCT reagent. Immunoassay for quantitative determination of PCT is a sandwich method with two antigen-specific monoclonal antibody, with a detection limit of 0.1ng/ ml and a total duration time of 18 min. PCT is stable in *vitro* and in *vivo* and only 30 microliter serum or plasma is needed for this purpose (7,8).

C-reactive protein (CRP) was measured by immunometric method in Immulite 1000.

Statistical analysis

For description of the numerical variables, the mean values and their respective standard deviations were reported. The difference between groups were assessed using the non-parametric Mann-Whitney U-test and correlation coefficients. A p-value of <0.05 was considered statistically significant in all cases.

Results

Table 1 presents the distribution of selected biochemical parameters in the study ample. As displayed in this table, the observed values for WBC,

PCT and CRP had a wide overlapping area in patients with bacterial and non-bacterial meningitis. At the moment of hospital admission, patients with bacterial meningitis had higher values of all parameters included in the study. PCT levels were statistically significantly elevated in all patients with bacterial meningitis (mean value: 22.47±28.1ng/ml) in comparison to PCT levels in patients with non-bacterial meningitis who had lower PCT levels (mean value: 0.83±0.46 ng/ ml).

PCT, CRP and leukocyte count were all positively correlated (data not shown), but these relationships were highly significant only in the bacterial meningitis group. A PCT concentration of >2ng/ml had 100% sensitivity and negative predictive values in bacterial meningitis.

Table 1. Distribution of selected biochemical parameters in the examined patients

Parameter	Bacterial meningitis (n=20)		Non-bacterial meningitis (n=12)		P-value
	Mean value	Standard deviation	Mean value	Standard deviation	
WBC	20.1730	5.222	14.954	2.556	<0.001
PCT	22.4755	28.4098	0.8382	0.4653	<0.001
CRP	176.4625	73.8939	34.7667	22.4613	<0.001
IL-6	288.7450	351.8021	16.7583	10.7506	<0.001
TNF-alpha	162.1800	299.4984	21.1167	25.8940	<0.001

Discussion

A good marker for bacterial infection should fulfill the following criteria: early diagnostic and prognostic values and should be additionally helpful for therapeutic antimicrobial decisions (10,11).

In this study, we found that serum PCT levels are exclusively higher in patients with bacterial meningitis. Mean values in these patients were 22.4 ng/ m and lower values 2.25 ng/ ml, compared to mean values 0.83 ng/ ml and high values 1.46 ng/ ml in non-bacterial meningitis.

Our results demonstrate that, the higher value of PCT in non-bacterial meningitis is still low compared with lower value of PCT in bacterial meningitis. Even CRP and total leukocyte count are helpful to discriminate bacterial meningitis from non-bacterial meningitis, but our results indicate that concentration of CRP should be low in the first days of bacterial meningitis.

On the other hand, in non-bacterial meningitis there should be verified considerable values of CRP. High values of PCT correlate with severity of infection and the presence of the organ dysfunctions. Our results correlate with other studies that concluded that PCT and CRP had diagnostic value in diagnosis of bacterial meningitis in patients with CSF pleiocytosis, with higher sensitivity for PCT (2,3).

In conclusion, serum procalcitonin level must be used in early diagnosis of bacterial meningitis with higher sensitivity than other traditional parameters. PCT appears to be a reliable biomarker in differential diagnosis between bacterial and non-bacterial meningitis, and diminishes the value of lumbar puncture performed 48-72 hours after admission to assess treatment efficacy.

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