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The ability of Serum procalcitonin to predict Bacterial versus viral meningitis

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Abstract

Background: Meningitis is a life-threatening inflammatory disease of the brain and spinal cord, mostly caused by bacterial and viral infections. Because of the high mortality rate and the possibility of neurological sequelae in survivors, a quick diagnosis with near 100% sensitivity is critical for patients with bacterial meningitis. New biomarkers like procalcitonin may help design an accurate decision tool for the diagnosis of such a condition. The validity of serum procalcitonin in distinguishing between acute bacterial and viral meningitis was evaluated.

Method: 40 Adult patients (17 with bacterial and 23 with viral meningitis) were included in this Prospective correlational diagnostic yield study. A non-parametric test was used for hypothesis testing. Sensitivity, specificity, and predictive values for several laboratory parameters were calculated.

Result: The median serum procalcitonin level in patients with bacterial meningitis was 1.5 ng/ml (range 0.2-25 ng/ml) and in the group with viral meningitis 0.08 ng/ml (range 0.01-0.2 ng/ml). A serum procalcitonin level > 0.1 ng/ml had a 94% positive predictive value for bacterial meningitis and a 100% negative predictive value.

Conclusion: Serum procalcitonin concentrations > 0.1 ng/ml appear to be a reliable indicator of bacterial CNS infection, with high positive predictive values and maximum negative predictive values.

Keyword: Procalcitonin, meningitis, Serum, Viral, Bacterial, predictive value

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Introduction

Acute bacterial meningitis remains a substantial source of morbidity and mortality despite advances in antibiotic therapy, with 1.2 million cases per year, resulting in 135 000 death worldwide in 1998 (1).

In the United States, the incidence of meningitis changed by -31% from 2.00 cases per 100,000 population in 1998-1999 to 1.38 cases per 100,000 population in 2006-2007. The case fatality rate did not change significantly: it was 15.7% in 1998-1999 and 14.3% in 2006-2007 (2). Bacterial meningitis necessitates immediate medical attention (3).

Acute meningitis is suggestive in almost all patients presented with at least two of the following symptoms: fever, headache, neck stiffness, and altered mental status (4). Because of the high mortality rate and the possibility of neurological sequelae in survivors, a quick diagnosis with nearly 100 percent sensitivity is critical. (5).

For individuals with suspected meningitis, a CSF examination is a critical part of the diagnostic process. A CSF glucose of less than 40 mg/dl, A CSF: serum glucose ratio of less than 0.4, a CSF protein concentration of more than 50 mg/dl, and a CSF WBC count of more than 5 cells/μL, have been acknowledged as individual markers for bacterial meningitis with a high risk of occurrence (5).

The causal culprit is discovered in 60–90% of purulent meningitis cases using a Gram stain investigation of CSF and CSF culture. (6).

Routine blood and CSF information, on the other hand, can sometimes fail to distinguish 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 (7).

CRP has long been considered a biomarker for inflammation. However, CRP may indicate a delayed rise during the course of bacterial infection, leading to false-negative testing in the early stages of the disease (8). CRP can be raised as a result of viral infections, making it difficult to distinguish between bacterial and viral causes of meningitis (9).

Due to its great diagnostic accuracy in a variety of infectious diseases, such as sepsis, acute infectious endocarditis, and pancreatitis, procalcitonin (PCT) is presently regarded as the best contender to replace CRP (10). Procalcitonin (PCT), a calcitonin propeptide, is thought to be

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produced in C cells of the thyroid gland and secreted by peripheral blood leukocytes (11). Normal PCT levels in healthy individuals are <0.1 ng/ml, and levels increase dramatically in response to bacterial infection (12). This rise is thought to be related to CALC-1 gene overexpression and enhanced PCT release from multiple tissues in response to bacterial endotoxins and inflammatory cytokines such as TNF-, IL-6, and IL-1 (13). Unlike CRP, PCT is not raised in viral infections, giving it the valuable ability to distinguish between bacterial and viral causes (14).

There have been only a few reports in the literature on serum PCT as a marker of bacterial meningitis. According to Gendrel et al., measuring the plasma PCT level can help distinguish between bacterial and viral meningitis in infants (15). And adult (16)(17)(18).

The study aims to validate the efficacy of procalcitonin in the differential diagnosis of viral and bacterial meningitis.

Methods

Forty adult patients with acute meningitis admitted in 2020-2021 to Al-Imamain Al-Kadhimain medical city and Baghdad teaching hospital, were included in this prospective correlational diagnostic yield study. The study protocol was approved by the Department of Neurology of the Iraqi medical board.

Inclusion criteria: Adult patients presented with a history and physical examination suggestive of acute meningitis.

Exclusion criteria: Patients received empirical antibiotics of more than three days and immunocompromised patients.

Blood samples were taken and a lumbar puncture was performed on all patients included in the study following admission to the hospital. Biochemical and cytological examinations of CSF samples were performed, including the measurement of leukocyte and differential 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. An immunoluminometric test (LUMItest PCT, BRAHMS Diagnostica, Berlin) was also used to evaluate PCT levels during admission (19). PCT values were not followed during the hospitalization. If samples were not analyzed within 4 h after CSF had been taken, they were stored at –20°C. The detection limit of this test is 0.1 ng/ml. PCT serum levels

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in healthy persons are less than 0.1 ng/ml, and values more than 0.5 ng/ml are deemed abnormally increased by this assay (19).

The criterion for the diagnosis of meningitis was the presence of an elevated CSF leukocyte count (more than 5 cells /μl) in a patient with the appropriate clinical features (20).

Meningitis was defined to be bacterial by the finding of predominant neutrophil pleocytosis and CSF/serum glucose ratio less than 0.4. On the other hand, Meningitis was defined to be viral by the finding of predominant lymphocytes pleocytosis and a normal CSF/serum glucose ratio of 0.4 or more. According to these criteria, patients were divided into a group with bacterial meningitis and a group with viral meningitis. No single value of any CSF or blood parameter can distinguish between bacterial and viral meningitis (21).

Since we had a small sample size, determining the distribution of the variables was important for choosing an appropriate statistical method. So, a Shapiro-Wilk test was performed and showed that the distribution of serum PCT departed significantly from normality ($W = 0.45$, p-value < 0.001). This was also true for the distribution of blood WBC count, ERS, CRP, CSF protein, CSF LDH, and CSF WBC count. Based on this outcome, a non-parametric test was used, and the median with the range was used to summarize the variables.

A comparison of the group with bacterial meningitis and the group with viral meningitis was made with the nonparametric Mann-Whitney Wilcoxon test for continuous variables and the Chi-square test for dichotomous variables. Google Sheets and R Statistical Packages were used for statistical analysis. and P values less than 0.05 will be considered to be statistically significant. For several laboratory parameters, sensitivity, specificity, and predictive values are calculated according to standard formulas.

Results

Out of the 40-sample included in our study, 17 were diagnosed with bacterial meningitis, and 23 were diagnosed with viral meningitis. The mean age was 37.9 ± 16.9. The male and female percentage is 68% and 32% respectively. The median Serum WBC count was 11 $x10^9$/L (range 6-22) and 8 $x10^9$/L (range 4-13), the median ESR was 33 mm/hr (range 13-66) and 20 mm/hr (range10-43), the median Serum CRP was 12 mg/L (range 6-22) and 7 mg/L (range 5-18), the median CSF: serum glucose ratio was 0.3 (range 0.16-0.6) and 0.7 (0.48-0.96), the median CSF protein was 118 mg/dl (range 25-600) and 60 mg/dl (range 15-205), the median CSF WBC

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count was 566 /cmm (18-25000) and 33 /cmm (13-335) in bacterial and viral meningitis group respectively.

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 groups were found for all laboratory parameters determined in this study.

In patients with bacterial meningitis, eight had a serum WBC count in the normal range, five had a CRP concentration < 10 mg/L, one had a CSF protein concentration < 45 mg/dl and four had a CSF: serum glucose ratio in the normal range.

In the group of patients with viral meningitis, four had serum WBC count > 11 $\times$ 10^9/L, three had a CRP level > 10 mg/L and sixteen had a CSF protein concentration > 45 mg/dl.

The median serum PCT level in patients with bacterial meningitis was 1.5 ng/ml (range 25-0.2 ng/ml). All 17 patients had a serum PCT above the cut-off value of 0.1 ng/ml.

The median serum PCT level in patients with viral meningitis was 0.08 ng/ml (range 0.2-0.01 ng/ml). Only one patient showed an abnormal serum PCT value of 0.2 ng/ml.

For the diagnosis of acute bacterial meningitis, the sensitivity, specificity, and predictive values of several laboratory parameters (further shown in table 2) are :

The Serum WBC count showed a sensitivity of 47%, a specificity of 87%, a positive predictive value of 73%, and a negative predictive value of 69%.

The ESR showed a sensitivity of 76%, a specificity of 52%, a positive predictive value of 54%, and a negative predictive value of 75%.

The Serum CRP showed a sensitivity of 71%, a specificity of 65%, a positive predictive value of 60%, and a negative predictive value of 75%.

The CSF: serum glucose ratio showed a sensitivity of 76%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 85%.

The Serum PCT showed a sensitivity of 100%, a specificity of 96%, a positive predictive value of 94%, and a negative predictive value of 100%.

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

	Bacterial Meningitis n = 17 median (range)	**Viral Meningitis n = 23 median (range)**	**P-value***
Age (years)	45 (17-73)	25 (18-66)	0.007
Gender (Male/Female)	12/5	15/8	0.72
Serum PCT (ng/ml)	1.5 (0.2-25)	0.08 (0.01-0.2)	< 0.001
Serum WBC count	11 (6-22)	8 (4-13)	0.001
Serum glucose	120 (80-280)	90 (65-200)	0.002
ESR	33 (13-66)	20 (10-43)	0.006
Serum CRP	12 (6-22)	7 (5-18)	< 0.001
CSF glucose	44 (20-102)	66 (40-120)	0.003
CSF: serum glucose ratio	0.3 (0.16-0.6)	0.7 (0.48-0.96)	< 0.001
CSF protein	118 (25-600)	60 (15-205)	< 0.001
CSF LDH	104 (22-510)	40 (20-98)	< 0.001
CSF WBC count	566 (18-25000)	33 (13-335)	< 0.001
CSF lymphocytes (%)	40 (2-80)	90 (73-100)	< 0.001
CSF neutrophil (%)	60 (20-98)	10 (0-27)	< 0.001

Normal reference laboratory values: blood WBC count 4.5-11 (10^9/L), RBS mg/dl, ESR 0-22 mm/hr. for Male, ESR 0-29 mm/hr. for Females, serum CRP <10 mg/L, serum PCT 0-0.1 ng/ml, CSF sugar is 50-80 mg/dl, CSF protein is 15-45 mg/dl, CSF LDH is up to 40 uL, CSF WBC <5 per mm^3.

* Mann-Whitney Test

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

	Sensitivity (%)	**Specificity (%)**	**Positive predictive value (%)**	**Negative predictive value (%)**
Serum PCT	100%	96%	94%	100%
Serum WBC count	47%	87%	73%	69%
ESR	76%	52%	54%	75%
Serum CRP	71%	65%	60%	75%
CSF: serum glucose ratio	76%	100%	100%	85%
CSF protein	94%	30%	50%	88%
CSF LDH	94%	65%	67%	94%
CSF WBC count	100%	0%	43%	0%

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Discussion

The biochemical features of CSF samples and clinical presentation have been used to diagnose bacterial meningitis. This prospective study found that blood procalcitonin levels may distinguish between acute bacterial and viral meningitis, and that serum procalcitonin levels have a greater sensitivity and specificity in the diagnosis of acute bacterial meningitis than other tests performed upon admission.

Serum samples were collected and PCT levels were evaluated on admission to assess the potential utility of PCT in predicting bacterial meningitis. PCT levels were observed to be elevated almost exclusively in patients with bacterial meningitis. As a result, our findings support earlier research linking higher PCT to bacterial meningitis rather than viral meningitis.

All cases collected in our study with bacterial meningitis had serum PCT levels above the cutoff value of 0.1 ng/ml, Gendrel et al. (15), who measured the plasma PCT level in 59 children with bacterial or viral meningitis, also found serum PCT level above 4.8 ng/ml in all 18 patients with bacterial infection, however, Schwarz et al. (18) found PCT levels in normal limits in five patients with bacterial meningitis and Jereb et al. (16) and Viallon et al. (17), found low serum PCT levels in two out of 20 (10%) and two out of 23 (8.7%) respectively in patients with bacterial meningitis.

The positive predictive value of serum PCT was 94%, and it was better than other parameters such as serum WBC count, serum CRP, and CSF WBC count, except for CSF: serum glucose ratio which was found to have 100% PPV. The negative predictive value of serum PCT was 100%, thus even higher than those found for other parameters routinely used in clinical practice.

Procalcitonin's mechanism and site of synthesis are still unknown. In one of the studies, healthy volunteers received an intravenous injection of endotoxin, which increased procalcitonin, and the authors speculate that leukocytes are the presumed source of procalcitonin production. (22).

The role of procalcitonin in the systemic inflammatory response is still unknown. In a small animal model of Escherichia coli peritonitis, Nylen et al. (23) found that procalcitonin infusion increases mortality. We don't know if procalcitonin is also a modulator of the systemic inflammatory response, even though it appears to be a useful marker of bacterial infection.

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CONCLUSION

This study concludes that serum PCT levels are reliable markers of bacterial meningitis. A PCT level > 0.1 ng/ml predicts bacterial infection of the CNS better than an elevated serum WBC count, serum CRP, ESR, and CSF protein concentration.

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