Serum Procalcitonin in Viral and Bacterial Meningitis

Usama M Alkholi, Nermin Abd Al-monem, Ayman A Abd El-Azim, Mohamed H Sultan

Department of Pediatrics, Zagazig University, Zagazig, Egypt

ABSTRACT

Background: In children with meningitis, there is a difficulty to verify the etiology as viral or bacterial. Therefore, intensive research has been carried out to find new and rapid diagnostic methods for differentiating bacterial from viral meningitis. **Objectives:** The aim of this work was to study the behavior of procalcitonin (PCT) and whether it can be used to differentiate children with bacterial from those with viral meningitis. We also compared PCT to C-reactive protein (CRP) and white blood cell count. **Patients and Methods:** Forty children aged from 4 months to 12 years with clinically suspected meningitis were studied. Lumbar punctures were done for all cases before starting initial antibiotic treatment. According to the results of bacterial cultures and cerebrospinal fluid (CSF) cytochemical profile, our patients were classified into two groups: bacterial meningitis group and viral meningitis group. PCT, CRP, and leukocyte count were measured at the time of admission and after 3 days. **Results:** PCT levels were significantly higher in patients with bacterial meningitis (mean, 24.8 ng/ml) compared to patients with viral meningitis (mean, 0.3 ng/ml) (P<0.001). PCT levels in bacterial meningitis group decreased after 3 days of starting treatment, but remained higher than viral meningitis group (mean, 10.5 ng/ml). All CSF parameters, blood leukocytes, and CRP showed overlapping values between the two groups. Serum PCT with cut off value >2 ng/ml showed sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 66%, 68%, and 100%, respectively, for the diagnosis of bacterial meningitis. **Conclusion:** Serum procalcitonin level has a better diagnostic and prognostic value than CRP or leukocyte count to distinguish between bacterial and viral meningitis. It is also a good indicator of the efficacy of treatment of bacterial meningitis.

Key words: C-reactive protein, Meningitis, Procalcitonin

INTRODUCTION

Despite the advances in diagnosis and treatment of infectious diseases, meningitis and encephalitis are still considered as important causes of mortality and morbidity. Early diagnosis and starting immediate empirical therapy are the key factors to reduce the morbidity and mortality related to bacterial meningitis.[1] The recommendations of early introduction of antibiotic treatment assure rapid treatment of children with bacterial meningitis but result in systematic hospitalization and antibiotic administration for children with aseptic meningitis, with the associated morbidity and economic burden. Therefore, distinguishing bacterial and aseptic meningitis in the emergency department could help to limit unnecessary antibiotic use and hospital admissions. Because the consequences of delayed diagnosis of bacterial meningitis can be severe, any proposed diagnostic tool must achieve near 100% sensitivity.[2] Clinical criteria, Gram staining, and bacterial antigen testing of CSF as well as the classic biological markers in the blood (CRP level, white blood cell count [WBC], and neutrophil count) or CSF (protein level, glucose level, WBC count, and neutrophil count) used alone do not offer 100% sensitivity with high specificity for distinguishing bacterial and aseptic meningitis.[2] Waiting for at least 2 days was recommended to identify bacterial growth in CSF cultures, whereas this period is 3–8 days for viral cultures.[3] Moreover, identifying the frequently encountered viral agents via polymerase chain reaction is not always possible in every institution. Therefore, intensive research has been carried out to find new and rapid diagnostic methods for differential diagnosis of bacterial and viral meningitis.[4] Procalcitonin (PCT), which is a calcitonin propeptide, is supposed to be synthesized in C cells of the thyroid gland and secreted from leukocytes of the peripheral blood. The secretion of PCT was found to increase in the presence of bacterial lipopolysaccharides and cytokines that are associated with sepsis.[5,6] It was previously shown that serum PCT levels increase during

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Address for correspondence:
Dr. Ayman A Abd El-Azim, E-mail: aymanazim@hotmail.com

the course of bacterial, parasitic, or fungal infections, but remain normal or slightly increase in viral infections and inflammatory reactions that are not infectious.[6,7] The aim of the present study was to determine the role of serum PCT levels in the early diagnosis of bacterial meningitis and to document their efficacy in the differential diagnosis of viral and bacterial meningitis.

PATIENTS AND METHODS

Forty children with meningitis admitted to Zagazig University Hospitals were enrolled in this prospective study in the period from July 2007 up to December 2007. The mean age was 5 years, and the age range was 4 months to 12 years. Twenty children were diagnosed as bacterial meningitis and the other 20 children as viral meningitis. The controls revealed by 10 children whose age range was between 6 months and 11 years. Informed signed consent was obtained from parents for their children to participate in the study.

Meningitis was diagnosed based on evaluation of history, physical examination, CSF laboratory findings, identification of bacterial agents in CSF, Gram staining, and cultures. Meningitis was defined as bacterial according to CSF laboratory findings (increased protein ≥2 g/l, decreased glucose ratio ≤0.4, and leukocyte count ≥1500 × 10/l and polymorph nuclear leukocyte domination), identification of bacterial agents in Gram staining, and/or positive bacterial culture. It was defined as viral if the viral culture, serological testing, pleocytosis, or reverse transcriptase polymerase chain reactions were positive, and the bacterial culture was negative.[2]

A control group of apparently healthy subjects were chosen and tested for serum PCT levels. Blood serum samples were taken from all cases at the time of diagnosis and at 72 h of treatment. The blood glucose level, peripheral leukocyte count, erythrocyte sedimentation rate, C-reactive protein and serum PCT in blood samples and the protein, glucose, number, and type of cells in CSF samples were simultaneously investigated. Symptoms and findings at the time of diagnosis, demographical data and follow-up body temperature of cases were monitored and recorded.

Collected serum and CSF samples were centrifuged at 2000 rotation for 15 min and stored at -80°C until the analysis. Serum PCT levels were studied by the immunoluminometric method in the Analyzer luminometer equipment using the Lumitest kit (Lumitest PCT kits BRAHMS Diagnostica, Berlin, Germany).

Statistical analysis of data was carried out using the SPSS 10.0 software. Differences between groups in continuous variables were tested for significance with the Mann–Whitney test. Differences in frequencies of findings between groups were analyzed by Fischer's exact test. The *P* value was considered significant if <0.05. Data were analyzed by sensitivity and specificity derived from the receiver operating characteristic (ROC) curve, and area under the ROC curve.

RESULTS

Clinical and demographic characteristics of patients are summarized in Table 1. Of the 40 cases with meningitis, 23 (57.5%) were males and 17 (42.5%) were females. The age of the patients was 65.2 ± 51.9 months (mean ± standard deviation). There was no difference between bacterial and viral meningitis groups in respect to mean age (*P* value>0.05). The most common symptoms at the time of diagnosis in all study groups were fever (100%), nausea or vomiting (55%), headache (45%), and convulsions (45%).

Bacterial culture revealed *Neisseria meningitides* in six cases, *Streptococcus pneumoniae* in six cases, *Haemophilus influenzae* in four cases, *Escherichia coli* in two cases, and *Pseudomonas aeuroginosa* in one case. Only one case was diagnosed as bacterial meningitis with a negative culture based on CSF finding and clinical picture. Three patients had viral meningitis while experiencing an episode of mumps, two developed the disease simultaneously with measles, and two showed viral meningitis during an episode of varicella, which were all verified by CSF serology. Additionally, reverse transcriptase polymerase chain reaction using previously defined primers detected the presence of RNA of enteroviruses in the CSF of 12 cases.

Table 2 showed significantly higher CSF leukocyte count with marked increase in the polymorphoneuclear leukocyte count in the bacterial meningitis group compared to the viral meningitis group (*P*<0.001). It also showed increased CSF proteins and decreased CSF sugar in bacterial meningitis group than viral meningitis group (*P*<0.01).

Serum PCT, CRP, and WBC count levels in all groups are summarized in Table 3. At the time of diagnosis, patients with bacterial meningitis had increased serum PCT, CRP, and WBC count compared with the control group (*P*<0.001). A similar comparison between bacterial and viral meningitis at the time of diagnosis also revealed increased serum PCT, CRP, and WBC count in bacterial meningitis patients (PCT, *P*<0.001; CRP, *P*<0.001; and WBC, *P*<0.001). However, the assessment of the same parameters at 72 h after the start of treatment showed

significantly higher levels of serum PCT, CRP, and WBC count in the bacterial meningitis group than in the viral meningitis group. After 72 h of the start of treatment, the decrease of serum PCT, CRP, and WBC count levels of the bacterial meningitis group was statistically significant compared with levels at the start of treatment ($P<0.05$).

Table 4 shows the sensitivity, specificity, positive, and negative predictive values of PCT and CRP for bacterial meningitis patients. Diagnostic cutoff levels with the optimum sensitivity and specificity were found to be PCT > 10 ng/ml and CRP > 20 mg/dl. A concentration of PCT > 2 ng/ml had 100% sensitivity and negative predictive value for bacterial meningitis, but with specificity and positive predictive value of only 60% and 68%, respectively.

DISCUSSION

When managing patients with meningitis, early diagnosis of the type of infection (bacterial or viral) is the element which has the greatest impact on clinical course, treatment, and patient survival. In this context, interest in markers that can differentiate bacterial from viral meningitis in children has been growing.[8] An ideal marker for bacterial infections should allow early diagnosis, inform about the course and prognosis of the disease, and facilitate therapeutic decisions. PCT covers these features best as compared to other commonly used biomarkers. A superior diagnostic accuracy of PCT has been shown for a variety of infections, e.g. respiratory tract infections, acute infectious endocarditis, shock, and pancreatitis.[9] Other authors have described "unconventional" inflammatory markers such as fibronectin, interleukin 6, tumor necrosis factor, and β-integrins, which have been used as research tools but not gained widespread acceptance in routine practice.[10]

Since Assicot and colleagues first proposed PCT as an early marker of bacteremia, descriptive reports of PCT measurements in children have been reported.[5] More recently, several authors have reported the quantitative evaluation of PCT as a diagnostic marker of bacteremia and fungemia, quoting sensitivity and specificity ranging from 57% to 100% and from 50% to 100%, respectively.[11-13] Interpretation of the literature dealing with PCT is complicated by variation in the choice of the "abnormal" cutoff value, and by the diverse age range and nature of the study populations.[14]

In this study, a significant increase was found in the serum PCT of bacterial meningitis cases at the time of diagnosis in comparison with that of the viral meningitis group and the control group. PCT levels measured after 72 h of the start of treatment were found to be less than the level measured at the beginning of treatment, but did not return to normal values. This finding suggests that the serum PCT level continues to be high for 72 h (despite treatment) and can be used for diagnosis for at least 72 h. Nevertheless, it is more reliable in diagnosis when measured before starting any treatment. Normally, PCT level is very low in the circulation or in the serum of healthy subjects as well as in patients with inflammatory diseases, reaches high concentrations in patients with severe bacterial infection. It decreases rapidly after appropriate antibiotic therapy. This result is in agreement with that obtained by many investigators.[2,15-17] They found that PCT concentration increased in bacterial meningitis with or without shock, but remained low in viral meningitis and inflammatory

Table 1: Clinical and demographic features of all groups

	Bacterial meningitis	Viral meningitis	Control group
Gender			
Male	10 (50)	13 (65)	4 (40)
Female	10 (50)	7 (35)	6 (60)
Age (months)	60.6 ± 25	70.5 ± 30	60 ± 26
Clinical findings			
Fever	20 (100)	16 (80)	
Nausea or vomiting	12 (60)	11 (55)	
Headache	9 (45)	5 (25)	
Convulsion	9 (45)	10 (50)	
Parotitis	0 (0.0)	3 (15)	
Meningeal irritation signs	5 (25)	4 (20)	

Figures in parentheses are in percentage

Table 2: Laboratory findings of all groups

	Bacterial meningitis	Viral meningitis	*P* value
CSF leukocyte count (cells/mm³)	940 ± 256	170 ± 125	< 0.001
CSF differential leukocyte count fraction (%)	0.75 ± 30	0.17 ± 0.12	< 0.001
CSF protein (mg/dl)	2.02 ± 1.3	0.5 ± 0.19	< 0.01
CSF glucose (mmol/l)	1.7 ±1.2	3.1 ± 0.9	< 0.01

Table 3: Serum PCT, CRP and WBC count in all groups

	Bacterial meningitis		Viral meningitis		e -Control group	*P* value
	a–At time of diagnosis	b–After 72 h	c–At time of diagnosis	d–After 72 h		
Procalcitonin (ng/ml)	26.8 ± 12	10.8 ± 5.3	0.4 ± 0.2	0.3 ± 0.1	03 ± 0.1	*P*<0.001, a and b, a and c, and e, b and d a
CRP (mg /dl)	24.4 ±12.1	28.6 ± 12	4.9 ± 2.4	3.8 ± 1.6	2.5 ± 1.2	*P*<0.001 a and c, a and e, and *P*>0.05 a and b
WBC count (mm³)	18.4 ± 9.1	12.6 ± 5.8	8.6 ± 4.2	6.9 ± 3.4	6.6 ± 2.9	*P*<0.001 a and c, a and e *P*<0.05 a and b

PCT: procalcitonin, CRP: c-reactive protein, WBC: White blood cell

Table 4: Sensitivity, specificity, positive, and negative predictive values (%) of admission PCT and CRP values for bacterial meningitis patients

Screening value	Sensitivity	Specificity	PPV	NPV
PCT > 2 ng/ml	100	66	68	100
PCT > 10 ng/ml	88	84	82	90
CRP > 10 mg/dl	90	62	66	88
CRP > 20 mg/ml	76	80	76	80

PCT: procalcitonin and CRP: c-reactive protein

diseases. Taskin *et al.* who studied serum PCT and CSF cytokines found increased serum PCT and CSF cytokines in children with bacterial meningitis compared to those with viral meningitis.[1] Serum PCT measurement does not require any invasive intervention such as lumbar puncture and with its stable molecular structure in serum, it can be frequently measured in serum for the diagnosis and follow-up of bacterial meningitis, making this parameter more useful than CSF cytokines in clinical practice.[1]

It has been long known that CRP and leukocyte count can differentiate bacterial and viral infections especially meningitis. Our study showed a significant difference in the mean CRP and leukocyte count between bacterial and viral meningitis groups. This is in agreement with the results obtained by other investigators.[14,17,18] They found that CRP level and leukocyte count are valuable in differentiating between bacterial and viral infections. However, initial CRP levels can occasionally be low in bacterial disease, especially in the early stages.[19] High CRP levels have been observed in some cases of viral meningitis.[20] On the other hand, in our study and studies done by others,[21-23] PCT level has never been high in cases with viral meningitis and its level rises dramatically and quickly in response to bacterial infection, making it as more sensitive and specific than CRP as a marker of systemic bacterial infection in children. Furthermore, PCT concentrations start to rise from about 4 h after single endotoxin challenge, peak at about 6 h, and remain increased for over 24 h.[14,23] In contrast, CRP concentrations begin to rise between 6 and 12 h and reach a peak level only at 24 to 48 h.[24]

Although the diagnostic value derived from this study indicates the optimum combination of sensitivity and specificity, this value might not be the most useful, because a clinician might wish to identify all patients with serious disease at the expense of a high false-positive rate. We point out that a PCT concentration >2 ng/ml has 100% sensitivity and negative predictive value, although only 66% specificity and 68% positive predictive value, respectively, for bacterial meningitis in our study population. It follows that a PCT value of 2 ng/ml helps to distinguish bacterial from viral meningitis. For CRP of >10 mg/l, the sensitivity, specificity, positive predictive value, and negative predictive value are 90%, 62%, 66%, and 88%, respectively. Comparison between both parameters showed superiority of PCT over CRP in diagnosis.

Follow-up of our studied cases showed a significant decrease in PCT levels on third day after antibiotic treatment. This result is consistent with that obtained with many studies.[23,25-27] All found that serum PCT decreased to a very low or even unidentifiable level with treatment, making it a valuable parameter for evaluating the efficacy of antibiotic treatment. Assicot *et al.*[5] demonstrated a rapid decrease in PCT concentration with antibiotic treatment and hence the need for lumbar puncture performed 48–72 h after admission to assess treatment efficacy. Therefore, it can be measured frequently in the serum for follow-up of bacterial meningitis cases.

CONCLUSION

The use of biomarkers to distinguish between children with aseptic meningitis and life-threatening bacterial meningitis has been pursued for many years without significant changes to the routine evaluation of such patients. Indeed, the catastrophic consequences of making the wrong diagnosis in this setting mean that it is unlikely that any single test will be sufficiently sensitive to conclusively distinguish aseptic from bacterial meningitis. The authors, however, make a compelling case for the addition of serum PCT to the routine evaluation of acute meningitis, on the basis of the findings that PCT is certainly similar and may even be slightly superior to other single laboratory tests in current use for the evaluation of meningitis.

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