Role of Procalcitonin in Diagnosis of Meningitis

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Abstract

**Background:** Meningitis is a significant cause of morbidity and mortality worldwide. Cerebrospinal Fluid (CSF) analysis is the current gold standard for diagnosis. However, this test does not achieve a high enough sensitivity and specificity to distinguish between bacterial and viral meningitis. So, an urgent need for rapid diagnosis with a higher sensitivity is recommended.

**Aim of the Work:** To assess clinical usefulness of CSF PCT in diagnosis of septic versus aseptic meningitis.

**Subjects and Methods:** This study was conducted after formal consent on 60 patients (pts) presented with a picture of meningitis. They were divided into: Group I (GI) (30pts with bacterial meningitis), GI (30pts with viral meningitis) and GI11 controls: 30pts undergoing spinal anesthesia for non-neurological operations.

**Results:** CSF leucocytes and PMN% were higher in bacterial than viral group. Also protein content was higher, while sugar was lower in bacterial versus viral group. The most common pathogen causing bacterial meningitis according to culture was S. pneumoniae (36.7%), Meningococci (23.3%) and H. influenza (10.0%). The least common pathogens were Staph (3.3%) & E-coli (3.3) and culture was negative in (23.3%). CSF procalcitonin level was significantly higher in bacterial meningitis than viral meningitis with mean value 384.1 versus 281.1 (pg/ml) with p=0.006. Both meningitis groups had also significantly higher levels of PCT than the controls (186.6 pg/ml) with p<0.001. ROC curve showed that CSF PCT at level ≥216.74pg/ml is diagnostic of meningitis with sensitivity 83.3%, specificity 66.7%, Positive Predictive Value (PPV) 83.3% and Negative Predictive Value (NPV) 66.7% and AUC (0.83). At level ≥295.4pg/ml PCT is diagnostic for bacterial meningitis with sensitivity 76.7%, specificity 68.3%, PPV 71.8%, NPV 75% and AUC 0.8. At level <295.4 pg/ml PCT is diagnostic for viral meningitis with sensitivity (73.3%), specificity (63.3%), PPV (66.7%) NPV (70.4%) and AUC (0.7).

**Conclusion:** CSF PCT can be used as a diagnostic test for differentiation between bacterial and viral causes of meningitis.

**Key Words:** Meningitis – C reactive protein – Procalcitonin – Diagnosis.

**Introduction**

MENINGITIS is a life-threatening inflammatory disease of the meninges that can be triggered by infectious or noninfectious causes. Infectious meningitis is sub-divided to non-bacterial and bacterial meningitis. Non-bacterial meningitis is usually caused by viral or fungal infections [1]. If not treated, it can lead to permanent disability, coma, and even death. To reduce the morbidity and mortality related to bacterial meningitis, it is important to differentiate bacterial meningitis from aseptic meningitis during the acute phase of the disease, when the clinical symptoms are often similar [2]. The clinical criteria and classic biological markers in the blood or CSF used alone do not offer 100% sensitivity with high specificity for distinguishing bacterial and aseptic meningitis [3]. Procalcitonin is considered as a marker of bacterial infections including meningitis [4]. The normal physiological level of procalcitonin in serum is less than 0.1ng/ml. This value can increase several folds in systemic bacterial infections [5]. It was previously shown that serum PCT levels increase during 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]. Numerous studies have compared the diagnostic and prognostic usefulness of PCT with other inflammatory markers [7]. However, only few studies have addressed the value of PCT levels in CSF in meningitis and presented conflicting results. Several authors have reported the quantitative evaluation of PCT as a diagnostic marker of bacterial meningitis [8-11].

**Subjects and Methods**

This cross sectional study was conducted on 60 patients with clinical picture of meningitis admitted to Shebin El-Kom Fever Hospital and Shebin El-Kom Educational Hospital during the period from December 2014 to September 2015.
They included 38 males and 22 females and their ages ranged from 18 to 65 years old. These patients were classified according to the results of clinical data and CSF findings into 30 patients as septic meningitis group (GI) and 30 patients as aseptic meningitis group (GII). Additionally, 30 cases of matched age and sex free of any CNS diseases undergoing spinal anesthesia for non-neurological operations were included in the study as GIII (control group). Informed consent was taken from all study population before taking CSF samples. In patients presented with coma or disturbed consciousness, consent was taken from their first degree relatives. Septic meningitis was diagnosed in patients with CSF pleocytosis (CSF leukocyte count >5 cells/µl) and one of the following criteria: (1) Positive CSF Gram-stained smear for a bacterial pathogen, (2) Positive CSF culture for a bacterial pathogen, or (3) Positive blood culture [12]. Diagnostic criteria for aseptic meningitis were presence of more than five leukocytes in cubic millimeter of cerebrospinal fluid with the dominance of lymphocytes, moderate CSF total protein increase and normal or slightly reduced glucose [13]. Culture negative cases were considered as aseptic [14]; viral [8]; or meningitis of unidentifiable cause [15]. Patients with the following conditions were excluded: Age less than 18 years old, traumatic CSF puncture, cerebrovascular stroke and malignancy. All patients were subjected to full history taking, thorough clinical examination and investigations including complete blood count, kidney function tests, random blood sugar, ESR and CRP, serum transaminases and finally, lumbar puncture for CSF examinations for physical examination (tension and aspect), chemical analysis (CSF protein and glucose) and microscopic examination (cell counting, bacteriological gram staining and culture).

**CSF Procalcitonin (PCT) measurement:** Was done Using Human Procalcitonin (PCT) ELISA Kit. The kit uses a double-antibody sandwich Enzyme-Linked Immunosorbent Assay (ELISA) to assay the level of Human Procalcitonin (PCT) in (serum, plasma, urine, CSF and tissue samples). Procalcitonin (PCT) was added to monoclonal antibody Enzyme well which is pre-coated with Human Procalcitonin (PCT) monoclonal antibody, incubation; then, Procalcitonin (PCT) antibodies labeled with biotin was added, and combined with Streptavidin-HRP to form immune complex; then incubation and washing was carried out again to remove the uncombined enzyme. Then Chromogen Solution A, B were added, the color of the liquid changes into the blue. And at the effect of acid, the color finally becomes yellow. The chroma of color and the concentration of the Human Substance Procalcitonin (PCT) of sample were positively correlated. (BRAHMS PCT instruction manual, 2007).

**Statistical analysis:** The collected data were tabulated and analyzed using SPSS Version 16 software (Spss Inc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean ± standard deviation, median and range. Chi square test (χ²) or Fisher’s Exact Test (FET) were used to analyze categorical variables. Quantitative data were tested for normality using Shapiro test assuming normality at p>0.05. ANOVA test was used to analyze normally distributed variables among 3 independent groups. While non parametric variables were analyzed using Man Whitney U-test for 2 independent groups, Kruskal Wallis Test (KWT) for 3 independent groups. Spearman’s correlation coefficient (rho) was used to assess correlation between non parametric variables. ROC curve analysis was used to detect cutoff values of procalcitonin with optimum sensitivity and specificity in early diagnosis of meningitis and differentiating BM from VM. The accepted level of significance in this work was stated at 0.05 (p<0.05 was considered significant).

**Results**

The present study was conducted on 90 subjects (55 male and 35 female). Their ages ranged from 18 to 65 years old with a mean age of 34.0±12.9 years. The study populations were subdivided into three groups (septic meningitis, aseptic meningitis and healthy control groups). The results illustrated that no statistically significant difference between the septic and aseptic meningitis groups regarding the socio-demographic data and the clinical picture apart from the presence of neck rigidity, positive Kering’s and Brudzninski signs that were more frequent in bacterial meningitis than viral meningitis group. Hemoglobin concentration, WBC Count and PMN% were significantly higher in septic meningitis than aseptic meningitis group (p<0.001). There was no statistically significant difference between the two meningitis groups as regard ESR, blood sugar, urea, creatinine, ALT and AST (p = 0.41). Regarding the CSF characters, a highly significant increase in CSF protein & CSF total leukocytic count and a highly significant decrease in CSF glucose in group I patients when compared to group II. Moreover, PMN cells % were significantly more predominant in septic meningitis group than in aseptic meningitis group. CSF culture was positive in 23 patients of GI (76.6%) while it was
negative in 7 patients of the same group (23.3%). CSF culture results revealed that the most frequently detected organisms were St. pneumoniae (47.8%), meningococci (30.4%), H. influenza (13.04%), Staph. aureus in one patient (4.34%) and E. coli in one patient (4.34%). The results of this study revealed CSF procalcitonin levels were significantly higher in septic meningitis group than the aseptic meningitis group with a mean of (384.1 pg/ml) versus (281.1 pg/ml) and both were significantly higher than that of the control (198.2 pg/ml). The ROC curve showed that CSF procalcitonin level at a cut off value more than 216.74 pg/ml have a sensitivity of (83.3%) and specificity of (66.7%) in distinguishing patients with meningitis from those without with positive predictive value (PPV) 83.3%, and Negative Predictive Value (NPV) 66.7% and AUC=0.83. However, at a cut off value more than 295.4 pg/ml, it can differentiate septic from aseptic meningitis with a sensitivity of (76.7%) and specificity of (68.3%) with PPV and NPV of 71.8% and 75% respectively and AUC= 0.8. There was a statistically significant positive correlation between CSF PCT level with CSF Leucocytes ($p<0.001$), CSF PMN cells ($p<0.001$) and CSF protein ($p=0.002$).
Table (3): Correlation between CSF Procalcitonin and the studied variables among the two meningitis groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Procalcitonin (n=60)</th>
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<tbody>
<tr>
<td></td>
<td>rho</td>
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<tr>
<td>Age</td>
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<tr>
<td>Duration</td>
<td>0.05</td>
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<tr>
<td>Temperature</td>
<td>0.181</td>
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<tr>
<td>SBP</td>
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<tr>
<td>DBP</td>
<td>0.033</td>
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<tr>
<td>Hb%</td>
<td>0.108</td>
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<tr>
<td>PLTs</td>
<td>0.045</td>
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<tr>
<td>WBCs</td>
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<tr>
<td>PMN%</td>
<td>0.141</td>
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<tr>
<td>CRP</td>
<td>0.220</td>
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<tr>
<td>ESR</td>
<td>0.074</td>
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<tr>
<td>Blood sugar</td>
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<tr>
<td>Urea</td>
<td>0.018</td>
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<tr>
<td>Creat</td>
<td>0.073</td>
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<tr>
<td>ALT</td>
<td>0.01</td>
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<tr>
<td>AST</td>
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<tr>
<td>CSF Leucocytes</td>
<td>0.580</td>
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<tr>
<td>CSF PMN</td>
<td>0.462</td>
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<tr>
<td>CSF Protein</td>
<td>0.395</td>
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<tr>
<td>CSF Glucose</td>
<td>-0.188</td>
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</tbody>
</table>

Discussion

Used alone, no single clinical criterion offers 100% sensitivity with high specificity for distinguishing between bacterial and viral meningitis, nor does any individual laboratory criterion (CSF gram staining, bacterial antigen testing, 'classic' blood markers such as ESR, White Blood Cell (WBC) or neutrophil counts or CSF markers such as, its protein and glucose levels or WBC and neutrophil counts [16]. Therefore, combinations of clinical and laboratory criteria is needed [17]. Many studies have investigated the diagnostic accuracy of serum PCT in meningitis. However, few published studies have focused on the value of PCT in CSF for diagnosis of BM and the differential diagnosis of BM from VM. While serum PCT is used in Europe for diagnosing BM as a routine biomarker, CSF PCT is not yet included in daily practice due to its cost and non-standardization of cut-off levels [18]. We evaluated the clinical usefulness of CSF procalcitonin in diagnosis of meningitis and differentiation between its bacterial and viral etiologies. In our study, CSF procalcitonin levels were significantly higher in septic meningitis group than the aseptic meningitis group and both were significantly higher than that of the controls. Using cut off value of 295.4pg/ml, CSF procalcitonin could distinguish patients with bacterial meningitis from those with aseptic meningitis with a sensitivity and a specificity of 76.7% and 68.3% respectively. When this cut off point decrease to (216.74pg/ml) it can also differentiate between meningitis and control group with a sensitivity and a specificity of (83.3%) and (66.7%) respectively. Similar results were reported by Konstantinidis et al., [19] who showed in their study relatively higher diagnostic value of CSF PCT test in patients with bacterial meningitis. Its sensitivity was 100%, specificity 96.43%, PPV 95%, and NPV 100%. In group with viral meningitis, sensitivity was 27.27%, specificity 96.43%, PPV 75%, and NPV 77.14%. According to Makoo et al., [20]. CSF procalcitonin level at cut off value of 0.5ng/mL had sensitivity of 100% specificity of 84.21%, positive predictive value of 88.88% and negative predictive value of 90.62%. Also [21] demonstrated CSF procalcitonin level at cut off value of 0.5ng/mL had sensitivity of 82% and specificity of 81% in diagnosis of bacterial meningitis.

An explanation for increased PCT levels in bacterial meningitis was a global increase of the first calcitonin gene (CALC-I gene) expression and a cardinal release of PCT from all parenchymal tissues and differentiated cell types throughout the body induced by a microbial infection [22]. So,
PCT is a considered a well-recognized marker for bacterial infection [23-24]. On the other hand Gendrel et al., [25] measured the plasma and CSF procalcitonin levels in 59 children who were admitted with bacterial or viral meningitis and reported that CSF PCT was not detected in children with bacterial meningitis. Similar results were presented by Vi-allon et al., [26] who compare between CSF and serum levels of procalcitonin in 105 consecutive patients. They concluded that there was a sufficient evidence to suggest the use of PCT in CSF for the diagnosis of bacterial meningitis.

Several studies had confirmed that a high serum PCT level is a good biological predictor for distinguishing between bacterial and aseptic meningitis. Prasad et al., [4] reported that, the mean level of serum PCT in patients with septic meningitis and control group was (22,669.21 ± 7,656.45pg/ml) and (3,943.8 ± 632.27pg/ml) respectively and showed a highly significant difference among both groups (p <0.001). The same study show a highly significant difference between serum PCT of aseptic meningitis and control groups. Also Vikse et al., [27] reported that Serum PCT is a powerful diagnostic test for the assessment of suspected meningitis, allowing rapid differentiation between bacterial and viral aetiologies, and earlier initiation of appropriate and necessary therapies. Kepa et al., [28] in a study carried out on 17 adult patients with acute bacterial meningitis and 16 patients with viral meningitis measured the levels of serum and CSF procalcitonin and concluded that using serum procalcitonin is a key element in differentiating bacterial meningitis from viral meningitis. Ray et al., [29] in a prospective study carried out on 151 adult patients with meningitis signs concluded that laboratory test results of cerebrospinal fluid are of moderate importance in differentiating bacterial meningitis from the non-bacterial meningitis in cases which Gram staining for bacteria is negative in the beginning however serum procalcitonin is an excellent predictive factor for differentiating acute bacterial meningitis. A recent meta-analysis involving a total of nine studies and 725 patients (192 BM and 533 VM) confirms this strong discriminatory power of PCT, with sensitivity of 90% and specificity of 98% [27].

We compared the diagnostic value of the two markers-CSF leucocytes and protein-with CSF procalcitonin level. Our results revealed that CSF leukocytic count shows a sensitivity of 93.3% and a specificity of 88.3% in the diagnosis of bacterial meningitis with a positive predictive value 80% and negative predictive value 96.4%. Comparison between CSF procalcitonin and CSF protein showed a sensitivity of 76.7% versus 83.3% and a specificity of 68.3% versus 93.3% respectively in diagnosis of bacterial meningitis. Jereb et al., [10] reported that CSF leukocyte count showed a sensitivity of 35% and a specificity of 100%, a predictive value was 100% and a negative predictive value 66% in the diagnosis of bacterial meningitis. They compared between CSF procalcitonin and CSF protein and revealed a sensitivity of 55% versus 70% and a specificity of 100% versus 96% respectively in diagnosis of bacterial meningitis.

**Conclusion:** CSF procalcitonin can be used as a diagnostic marker for differentiation between patients with bacterial meningitis and those with viral meningitis.

**References**

2876 Role of Procalcitonin in Diagnosis of Meningitis


دور البروكالسيتونين في تشخيص الالتهاب السحائي

الالتهاب السحائي هو سبب للإصابة والوفيات عالمياً، ويعد تحليل السائل النخاعي هو الأفضل لتشخيص الالتهاب السحائي بيد أنه لا يستطيع التمييز بدقة كاملة بين انتهاك السحايا البكتيري والفيروسي، ولذلك فنحن نحتاج ملحو لاختبار أكثر حساسية.

وتهدف هذه الدراسة إلى قياس نسبة البروكالسيتونين في السائل النخاعي وقدره في تشخيص الالتهاب السحائي والتمييز بين نوعية البكتيري والفيروسي.

وقد تم إجراء هذه الدراسة على 300 مريض يعانون من أعراض الالتهاب السحائي، ومن تقسم العدد الكامل للمشاركين بالدراسة إلى 200 مريض يعانون من الالتهاب السحائي البكتيري، و200 مريض يعانون من الالتهاب السحائي فيروسي. 20 شخص خضعوا للتخدير النقسي لأسباب غير العمليات الخاصة بالجهاز العصبي.

وقد أظهرت النتائج البحث أن عدد ألات الدم البيضاء والحالات مفصصة النواة في السائل النخاعي كانت أعلى في مرضى الالتهاب السحائي البكتيري عن الفيروسي وكذلك ارتفعت نسبة البروتينات في السائل النخاعي في المجموعة الأولى عن الثانية بينما انخفضت نسبة السكر في مرضى الالتهاب السحائي الرئيسي عن الفيروسي. كانت هذه النتائج أعلى في الفيروسي، بينما كانت المكورات المعدية الالتهابية في أقل الأسباب وارتفاع نسبة البروكالسيتونين في السائل النخاعي في مرضى الالتهاب السحائي البكتيري عن مرضى الالتهاب السحائي الفيروسي. كما كانت أعلى ارتفاعاً في كلا المجموعتين عن مجموعة التحكم. وقد أوضحت النتائج أنه يمكن استخدام قياس البروكالسيتونين في السائل النخاعي لتشخيص الالتهاب السحائي، كما يمكن بواسطة الفحص بين نوعية البكتيري والفيروسي.