

Serum Procalcitonin level and other biological markers in children with bacterial or non-bacterial meningitis

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ABSTRACT

Acute meningitis in children is predominantly aseptic and does not require specific treatment. However, meningitis has a bacterial origin in about 5% of patients and carries a risk of fatal outcome or severe neurological sequelae, especially when diagnosis and antibiotic administration are delayed. The objective of the present study was to evaluate the value of determining procalcitonin levels to discriminate between bacterial and non-bacterial meningitis in young children or infants and describe the variation in serum PCT levels over time during the treatment of meningitis.

A total of 50 children with meningitis admitted to a University Hospital were followed in this prospective study. Cerebrospinal fluid (CSF) and serum levels of procalcitonin were measured. The diagnosis of meningitis was based on clinical findings, gram staining, culture, and chemical analysis of CSF. Twenty-five children were diagnosed as bacterial meningitis and the other 25 children as non-bacterial Meningitis.

The mean procalcitonin level on admission in patients with acute bacterial meningitis was 18.3 ng/mL, and the lower level was 4.6 ng/mL, while the higher level in patients with non-bacterial meningitis was 0.62 ng/mL (mean level, 0.38 ng/mL). It is clear from the range of serum procalcitonin level that, there are no overlapping values seen for serum procalcitonin in both groups.

serum PCT levels can be used in the early diagnosis of acute bacterial meningitis and is more valuable than the other predictive marker. Similarly, they may be useful adjuncts in differential diagnosis of bacterial and non-bacterial meningitis and diminishing the value of 2nd lumbar puncture performed 48-72 hours after admission to assess treatment efficacy.

Keywords: Procalcitonin; Meningitis; Infection.

INTRODUCTION

Acute meningitis in children is predominantly aseptic and does not require specific treatment. However, meningitis has a bacterial origin in about 5% of patients [1-3] and carries a risk of fatal outcome or severe neurological sequelae, especially when diagnosis and antibiotic administration are delayed [4, 5]. Because distinguishing between bacterial and non-bacterial meningitis in the emergency department (ED) is some-times difficult, many recommend that antibiotic treatment be started immediately in children on clinical evidence of acute meningitis

and/or cerebrospinal fluid (CSF) pleocytosis and that treatment be continued until bacterial culture results become available 48 to 72 hours later [6, 7]. These recommendations assure rapid treatment of children with bacterial meningitis but result in systematic hospitalization and antibiotic administration for children with non-bacterial meningitis, with the morbidity and economic burden that accompany them [8-10]. Therefore, distinguishing between bacterial and non-bacterial meningitis in the ED 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 [11]. In untreated bacterial meningitis, Gram staining of CSF reveals bacteria in about 50-80% of cases and cultures are positive in at least 85% of cases. However, sensitivity of both tests is less than 50% in patients who are already on antibiotic treatment. Also, Clinical criteria [12-14] and bacterial antigen testing of CSF as well as the classic biological markers in blood (C-reactive protein [CRP] level, white blood cell [WBC] count, and neutrophil count) or CSF (protein level, glucose level, WBC count, and neutrophil count) [2,5,7,15] used alone do not offer 100% sensitivity with high specificity for distinguishing between bacterial and non-bacterial meningitis. Among new markers, serum procalcitonin (PCT) level [16] seems to be one of the most sensitive and specific predictors for discriminating between bacterial and non-bacterial infections [17, 18].

Procalcitonin (PCT), which is a calcitonin propeptide, is supposed to be synthesized in C cells of the thyroid gland [19] 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 [16, 20]. 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 [21, 22]. The objective of the present study was to evaluate the value of determining procalcitonin levels to discriminate between bacterial and non-bacterial meningitis in young children or infants and describe the variation in serum PCT levels over time during the treatment of meningitis.

MATERIALS AND METHODS

A total of 50 children with meningitis admitted to a University Hospital were followed in this prospective study. Twenty-five children were diagnosed as bacterial meningitis and the other 25 children as non-bacterial Meningitis. Informed signed consent was obtained from parents for their children to participate in the study. Meningitis was diagnosed according to evaluation of history, physical examination, CSF laboratory findings, identification of bacterial agents in CSF Gram

staining and cultures. Meningitis is defined as bacterial if the CSF laboratory findings (increased protein >2 g/l, decreased glucose ratio <0.4 , and leukocyte count >1500 / μ l and polymorph nuclear leukocyte domination), identification of bacterial agents in Gram staining and/or bacterial culture were positive; or was defined as non-bacterial meningitis if the acute onset of meningitis and the absence of any bacterial meningitis criteria. Blood serum samples were taken from all cases at the time of diagnosis and at 48-72 h of treatment. The blood glucose level, peripheral leukocyte count, erythrocyte sedimentation rate, qualitative CRP and serum PCT in blood serum samples and the protein, glucose and number and type of cells in CSF samples were simultaneously investigated. Symptoms and findings at the time of diagnosis, demographical data, peripheral leukocyte count, erythrocyte sedimentation rate, and follow-up body temperature (body temperature $>37.8^{\circ}$ C, armpit) of cases were monitored.

EDTA was added to blood samples obtained by venipuncture. Procalcitonin levels were measured in frozen samples (temperature, -20° C) in a blind manner by immunoluminometric assay (BRAHMS Diagnostica, Berlin). This assay, which is specific for the procalcitonin molecule, requires 20 μ L of plasma and can be done within 2 hours. Its detection limit is 0.1 μ g/L. Interassay and intraassay variations at both low and high concentrations are $<8\%$ and $<7\%$, respectively. Plasma procalcitonin levels in healthy children or adults, as determined with this assay, are <0.1 ng/mL. We measured levels of serum C-reactive protein (CRP) and CSF proteins and CSF cell counts by routine methods. Statistical analysis of data was carried out in a windows setting using the SPSS 16.0 program. Differences between groups in continuous variables were tested for significance with the Mann-Whitney test. Two-tailed $p \leq 0.05$ was considered significant.

RESULTS

Of the 50 cases with meningitis, 32 (64%) were males and 18 (36%) were females. The mean age was 59.16 ± 30.7 months and the age range was 4-158 months. (Table 1). There was no difference between bacterial and non-bacterial meningitis groups in respect to mean age ($p > 0.05$). Clinical characteristics and laboratory findings in both

groups are summarized in Table 1. The most common symptoms at the time of diagnosis in all study groups were fever (100%), nausea or vomiting (48%), Headache (42%) and convulsion (38%). The mean values and ranges for CSF leukocyte counts, CSF protein levels, glucose levels, and procalcitonin levels in both groups are shown in table 2. The differences in the mean values were highly statistically significant for any of the four tests. Bacterial culture revealed *Neisseria meningitidis* in 11 cases, *Haemophilus influenza* in 6 cases, *Streptococcus pneumoniae* in 5 cases, *Escherichia coli* in 2 case, and *Pseudomonas aeruginosae* in one case.

The mean procalcitonin level on admission in patients with acute bacterial meningitis was 18.3 ng/mL, and the lower level was 4.6 ng/mL, while the higher level in patients with non-bacterial meningitis was 0.62 ng/mL (mean level, 0.38 ng/mL). With a procalcitonin level of > 0.5 ng/mL as positive cut-off value, the sensitivity for diagnosis of bacterial meningitis was 100%, and the specificity was 96%, positive predictive value of 96% and negative predictive value of 100%. It is clear from the range of serum procalcitonin

level that, there are no overlapping values seen for serum procalcitonin in both groups.

Twenty-one patients with non-bacterial meningitis received an antibiotic as presumptive treatment for bacterial meningitis until the viral origin was determined. Six patients had pleocytosis (cell count, >1,000/ μ L). Initial procalcitonin levels ranged from 0.08 ng/mL to 0.62 ng/mL among these 21 treated children and were similar to the levels for other patients with non-bacterial meningitis who were not treated. Procalcitonin levels were measured during treatment in all patients with bacterial meningitis. In all cases, a marked decrease was observed after 72 hours. All patients had procalcitonin levels of <1 ng/mL at recovery (Figure 1).

Procalcitonin levels were measured in nine patients with non-bacterial meningitis on the second and third days. These levels always remained <1 ng/mL. Procalcitonin levels in blood and CSF samples collected at the same time were determined for all patients with bacterial meningitis and 16 patients with non-bacterial meningitis. No procalcitonin was found in the CSF samples.

Table 1. Clinical and demographic features of all groups

Parameters	Bacterial meningitis	non-bacterial meningitis
Gender (%)		
Male	15 (60)	17 (68)
Female	10 (40)	8 (32)
Clinical feature (%)		
Fever	25 (100)	25 (100)
Nausea or vomiting	10 (40)	14 (56)
Headache	12 (48)	9 (36)
Convulsion	10 (40)	9 (36)
Parotitis	0 (0.0)	7 (28)
Laboratory findings		
Erythrocyte sedimentation rate (mm/h)	31.2 \pm 22.8	18.4 \pm 9.5
Leukocyte count (/ μ L)	15000 \pm 2900	9500 \pm 1105

Table 2. CSF leukocyte counts, CSF protein levels, glucose levels, and procalcitonin levels in both groups

Parameters	CSF cells (/ μ L)	CSF protein (g/L)	CSF/ blood glucose ratio	Procalcitonin level (ng/mL)	Polymorph-nuclear leukocyte (/ μ L)	Lymphocyte count (/ μ L)
Diagnosis						
Bacterial meningitis	1460 \pm 970 (350 - 1750)	2.2 \pm 1.15 (0.35 - 3.7)	0.31 \pm 0.21 (0.11 - 0.47)	18.3 \pm 7.85 (4.6 - 34.1)	1371 \pm 745 (268 - 1330)	125 \pm 125 (20 - 160)
non-bacterial meningitis	410 \pm 312 (215 - 1050)	0.61 \pm 0.45 (0.1 - 0.97)	0.58 \pm 0.23 (0.45 - 0.83)	0.38 \pm 0.25 (0.01 - 0.62)	96 \pm 140 (11 - 120)	395 \pm 230 (200 - 980)
P-value	<0.001	<0.001	<0.01	<0.001	<0.001	<0.01

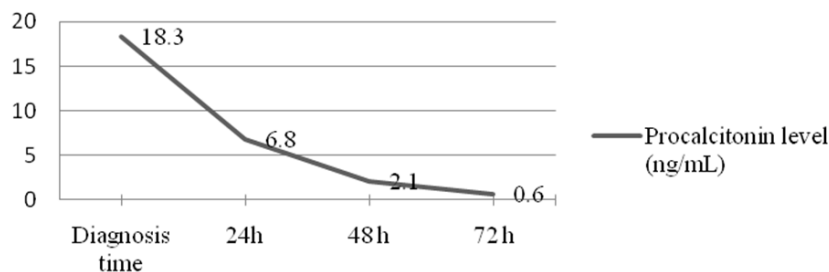


Figure 1. change in serum procalcitonin from admission to day 3 of treatment in bacterial meningitis group

DISCUSSION

A good biomarker for Bacterial infection should fulfill the following criteria; early diagnostic, prognostic value and helpful for therapeutic antimicrobial decisions [23, 24]. In the last few years, serum PCT level has been reported to be useful in the establishment of severe bacterial infections and in the follow up of treatment. In comparison to other commonly used tests, Procalcitonin appears to be a more specific and sensitive marker of a variety of infections, e.g. respiratory tract infections, meningitis, acute infectious endocarditis and pancreatitis. The role of PCT has also been extensively studied in the intensive care setting; here it is important that an accurate distinction made between inflammatory states and viral and bacterial infection [25, 26, 27]. To date, there have been only a few reports in the literature on serum PCT as a marker in the differential diagnosis of meningitis in childhood. In these studies, serum PCT was shown to be sensitive and specific with a range of 69-100% [28]. In the study reported by Schwarz *et al* [28], sensitivity of PCT was lower (69%). In our study, in confirm of previously studies, the sensitivity for diagnosis of bacterial meningitis was 100%, and the specificity was 96%.

In this study we found that serum procalcitonin levels were exclusively high in patients with bacterial culture positive meningitis, prior to treatment and became very low during follow up with treatment. Moreover, if we look at the PCT value, it is highly discriminate in all cases. The mean PCT level in patients with bacterial meningitis was 18.3 ng/ml, and the lower level was 4.6 ng/ml, while the higher PCT level in patients with non bacterial meningitis was 0.62 ng/ml and the mean was 0.38 ng/ml. It means that,

the highest value of procalcitonin seen in patients with non bacterial meningitis is still lower than the lower value of PCT seen in patients with bacterial meningitis. This result is in agreement with that obtained by many researchers. They found that PCT concentration increased in bacterial meningitis with or without shock, but remained low in viral meningitis and inflammatory diseases [24, 29, 30].

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 [31]. The largest tissue mass and major source of circulating PCT in sepsis is provided by Parenchymal cells (including liver, lung, kidney, adipocytes and muscle) and not the leukocyte population. The high serum PCT levels are seen in septic patients after near complete eradication of these leukocyte cells by antimicrobial therapy [32].

Procalcitonin levels measured at 48-72 h of the treatment were found to be less than the level measured at the beginning of treatment, but did not return to normal values as the healthy subjects at 48 h. This finding suggests that the serum PCT level continues to be high for 48 h (despite treatment) and can be used for diagnosis for at least 48 h. Nevertheless, it is more reliable in diagnosis when measured before starting any treatment. Normally, PCT is very low in circulation or in serum of healthy subjects as well as in patients with inflammatory diseases, reaches high concentrations in patients with severe bacterial infection and decreases rapidly after appropriate antibiotic therapy [33].

In this study, in accordance with the literature, gram staining of CSF was positive in only 52% of the bacterial meningitis cases, and culture was positive in 92%. For example, Marton and Gean (34) have shown that culture was positive in 60% – 90% of acute bacterial meningitis cases and fell to 40% – 60% in patients who had previous antibiotic therapy [35]. In bacterial meningitis, the CSF WBC count usually ranges between 1000 and 5000/ μ L, with a neutrophilic predominance, but, 10% of the patients with bacterial meningitis had a lymphocytic predominance [35], as in our study.

The estimation of the sensitivity and the specificity of CSF protein levels and ratio of glucose in CSF to glucose in serum in bacterial meningitis vary according to the study. In the diagnosis of acute bacterial meningitis, it was found that a CSF protein level >1 g/L gives a sensitivity and specificity of 82% and 98%, respectively [36], or a

CSF protein level >2 g/L gives a sensitivity and specificity of 86% and 100%, respectively [37].

Similar results were found in this study. The ratio of glucose in CSF to glucose in serum is widely used; in diagnosis of bacterial meningitis, a value >0.4 yielded a sensitivity and specificity of 80% – 91% and 96% – 98%, respectively [35, 36]. In conclusion, serum PCT levels can be used in the early diagnosis of acute bacterial meningitis and is more valuable than the other predictive marker. Similarly, they may be useful adjuncts in differential diagnosis of bacterial and non bacterial meningitis and diminishing the value of 2nd lumbar puncture performed 48-72 hours after admission to assess treatment efficacy.

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