Original Article

Diagnostic value of Serum Procalcitonin Levels in children with meningitis: a comparison with blood leukocyte count and C-reactive protein

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Abstract

Objectives: To determine the level of serum procalcitonin, blood leukocyte count (TLC) and C-reactive protein (CRP) in children with bacterial and non bacterial meningitis and document their efficacy in differential diagnosis. Also described are procalcitonin levels variation during treatment.

Methods: From March 2005 to February 2008, we evaluated 38 clinically suspected meningitis patients in the paediatric departments, Al-Jedaany Hospital, Jeddah, KSA, for Serum procalcitonin, CRP, TLC and Lumbar punctures and CSF analysis. Patients were classified into bacterial meningitis group I (18) and non bacterial meningitis group II (20).

Results: Serum PCT levels were significantly higher in bacterial meningitis (BM) {mean 4.8 ± 3.85 ng/ml (2.9-11.6)} compared with non bacterial meningitis (NBM) {mean 0.38 ± 0.25ng/ml(0.31-0.61)} {P< 0.001}. Mean of all CSF parameters, TLC {15,000 ± 2,900 cell/ml(BM) & 9,500 ±1,105 cell/ml(NBM)}and CRP {20 ± 6.8 mg/l (BM) & 12.5 ±12.0 mg/l(NBM)}showed a zone of overlapping between the two groups. There is a positive correlation between serum PCT, TLC and CRP in bacterial and non bacterial meningitis cases but this relation becomes highly significant with bacterial meningitis positive group. Day 3 and day 6 treatment serum PCT was less than on admission levels (P<0.001).

Conclusion: PCT can be used in the early diagnosis of bacterial meningitis and may be a useful adjunct in differentiating bacterial and non bacterial meningitis than CRP or TLC and diminishing the value of lumbar puncture performed 48-72 hours after admission to assess treatment efficacy.

Keywords: Serum procalcitonin level, Meningitis, Blood leukocyte count, C-reactive protein (JPMA 61:346; 2011).

Introduction

Meningococcal septicemia and meningitis remains is an important cause of morbidity and mortality in children despite the advent of highly effective bacterial conjugate vaccines. There is now good evidence that mortality from this disease is falling, but a high index of suspicion, prompt diagnosis, and aggressive management are essential to reduce mortality and morbidity.[1] It is becoming increasingly difficult to confirm the diagnosis of meningococcal infection by conventional microscopy and culturing techniques.[2]

Procalcitonin, 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.[3] In healthy subjects, circulating levels of PCT are below detection limits, increasing in patients with bacterial infections. Production of procalcitonin in the body during inflammation is linked with bacterial endotoxin and with inflammatory cytokines interleukin-6 and tumor necrosis factor (IL6 and TNF).[3] The increase of procalcitonin level is minimal in patients infected with viruses. In health, circulating concentrations of procalcitonin is very low, usually below 0.01 ng/ml and in viral infection and inflammation, the concentrations increase slightly but rarely above 1.0 ng/ ml.[4] It increases dramatically and quickly after single endotoxin injection, and this response is very rapid and the molecule is stable, making it a potentially useful marker for distinguishing bacterial from non bacterial infection.[5]

The present study was conducted to determine the level of serum procalcitonin, blood leukocyte count (TLC) and C-reactive protein (CRP) in children with bacterial and non bacterial meningitis and document their efficacy in differential diagnosis. Also described are procalcitonin levels over the time during the treatment of acute bacterial meningitis.

Methods

Thirty eight most likely meningitis children patients (22 males and 16 females), with ages ranging from 2 months to 10 years attending the paediatric departments of Al-Jedaani Hospital, Jeddah, KSA in the period from March 2005 to

February 2008 were included in this prospective study. The demographic and clinical characteristics of patients were recorded on admission. Meningitis was diagnosed according to history, physical examination, CSF laboratory findings, identification of bacterial agents in CSF gram staining and cultures. The studied patients were categorized according to the CSF bacteriological and cytochemical profile into the following two groups: Group I (Bacterial meningitis) comprised18 patients (10 males and 8 females), with ages ranging from 2 months to 10 years (mean age 4.3 ± 3.1 years). Meningitis was defined as bacterial if the CSF laboratory findings showed: (increased protein >2g/l, decreased glucose ratio <0.4, leukocyte count > 1500 × 10^6/l and polymorph nuclear leukocyte domination), identification of bacterial agents in gram staining and/or positive bacterial culture; and Group II (Non bacterial meningitis): included 20 patients (12 males and 8 females), with ages ranging from 2 months to 9 years (mean age 3.7±0.9 years) Patients were included in this group if no bacteria were documented on Gram-stain or bacterial culture of CSF, lymphocyte predominance of CSF cells, reduced protein level, and increased glucose ratio >0.5.[5]

Patients presenting with a further site of infection in addition to meningitis, or who had received prior antibiotic treatment for more than 2 consecutive days, were excluded from the study.

Our study was approved by the clinical ethics committee of the hospital and performed according to ethical procedures. A written informed consent was obtained from parents for the participation in our study.

All patients were subjected to full history, thorough clinical examination and the following tests: complete blood count, C-reactive protein, serum procalcitonin, and CSF cytochemical study and bacterial culture; i) Blood samples for procalcitonin measurement, C reactive protein, and leukocytes count were taken at time of admission (day 0), after 72 hrs (day 3) and after 6 days (day 6). Blood samples for procalcitonin were taken from the waste of blood taken for routine investigations. ii) Lumbar puncture was done by the anaestheologist before starting the initial antibiotic to detect total and differential leukocyte count, assay of proteins and glucose and for bacteriological study (gram staining and cultures and sensitivity).

Measurement of Complete blood count: It was done as a part of routine laboratory test by Cell- Dyne 1600 System (Abbott Park Laboratories, Ilinois, USA).

Measurement of serum Procalcitonin levels: An immunoluminometric assay (Brahms Diagnostica, Berlin, Germany) was used for the specific measurement of PCT in serum (detection limit, 0.10 ng/mL) according to the instructions of the manufacturer. The assay uses two antigen-specific monoclonal antibodies that bind PCT at two different binding sites. Luminescence was measured automatically by an analyzer (Behring Diagnostics, Marburg, Germany), and results were calculated using the software provided. Inter-assay and intra-assay variability were < 7% and 7%, respectively. At room temperature, the stability of PCT can be observed regularly in blood samples and can be measured together with routine variables. The results of Serum PCT can be obtained in 2 hours and only 20 µl of serum is needed.[5]

C-reactive protein was measured by enzymatic heterogeneous sandwich immunoassay. According to the manufacture manual (Vitro 950 analyzer, Johnson and Johnson, Rochester, New York, USA), It is a latex agglutination test for qualitative and semi-quantitative determination of CRP in serum. It is based on the immunological reaction between human CRP in the serum and the corresponding antihuman CRP antibodies bound to latex particles. The positive reaction is indicated by a distinctly visible agglutination of the latex particles in the test cell of the slide.

Statistical Analysis:

Descriptive statistical tests were expressed as mean ± standard deviation. The differences between the groups were evaluated using the non-parametric Mann-Whitney U test and correlation coefficient (r) with the threshold of significance set at $P < 0.05$.

Results

The demographic and clinical characteristics of the studied patients are summarized in Table-1 and shows that, there were no statistical differences in patient's demographic and clinical characteristics at time of admission. The type of organisms yielded from bacterial

Table-1: Patient characteristics on admission.

Characteristics	Group I Bacterial meningitis n = 18 No(%)	Group II Non bacterial meningitis n = 25 No(%)	P value
Mean Age (years)	4.3 ± 3.1	3.7 ±0.9	0.2
(Range)	(2mo-10 yr)	(2mo-9 yr)	
Sex (male)	10 (55%)	12(60%)	>0.05
(female)	8 (45%)	8(40%)	
Fever (>38°)	17(95)	18(90)	0.7
Headache	11 (61)	13(65)	0.4
Nuchal rigidity	13 (72)	11(55)	0.3
Seizures	3 (11)	2(10)	0.7
Purpura	3 (11)	2(10)	0.5
Focal neurological deficit	3 (11)	2(10)	0.3
Glasgow Coma Scale score (mean ± SD)	13 ± 2	13 ± 2	0.2
Bulging fontanelle,	4 (22)	3(15)	0.2
Positive Kernig & Brudzinski signs	7 (39)	9(45)	0.4

p>0.05 (Significant).

Table-2: Serum levels of procalcitonin, C-reactive protein and total leukocytic count of studied patients.

Test	Group	Group I Bacterial meningitis n = 18	Group II Non bacterial meningitis n = 20	P value
Procalcitonin	Mean ±SD	4.8 ± 3.85	0.38 ±0.25	0.001*
(ng/ml)	Range	(2.9-11.6)	(0.3-0.61)	
Total Leukocyte count (cell/ml)	Mean ±SD	15,000 ± 2,900	9,500 ±1,105	0.004*
	Range	(11,400- 18,600)	(8,400 11,200)	
C-reactive protein (mg/l)	Mean ±SD	20 ± 6.8	12.5 ±12.0	0.002*
	Range	(12.0-56.0)	(0.0-35.0)	
Total leukocyte count (cell/ml)	Mean±SD	1,460 ± 970	410 ± 312	0.003*
	Range	(350 -1,750)	(215 -1,050)	
Polymorph nuclear leukocyte (cell/ml)	Mean±SD	1,271± 835	95 ± 120	0.004*
	Range	(288 -1,380)	(10 – 110)	
Lymphocyte count (cell/ml)	Mean±SD	115 ± 135	390 ±210	0.01**
	Range	(20 -160)	(200 – 980)	
Protein (g/l)	Mean±SD	2.2 ± 1.15	0.61± 0.45	0.001*
	Range	(0.35 -3.7)	(0.1 -0.97)	
CSF/ blood glucose ratio	Mean±SD	0.31 ± 0.21	0.58 ± 0.23	0.02**
	Range	(0.11 -0.47)	(0.45 – 0.83)	

*P<0.001 **p<0.01

Table-3: Correlation of serum procalcitonin with total leukocyte count and C-reactive protein according to the type of meningitis.

Test	Procalcitonin	Group I Bacterial meningitis n = 18	Group II Non bacterial meningitis n = 20
Total Leukocyte count (cell/ml)	r	0.8817	0.5564
	p	0.001*	0.01**
C-reactive protein (mg/l)	r	0.6157	0.4419
	p	0.002*	0.04***

*p<0.001 **p<0.01 ***p<0.05

cultures of CSF are; Neisseria meningitides (five patients), Streptococcus pneumonia (five patients), Haemophilus influenza-b (four patients), E-coli (two patients), and Staphylcoccus aureus (two patients). The differences in the mean values and ranges for CSF parameters [cells, CSF protein levels, and CSF glucose/blood glucose ratio], blood leukocyte, CRP and procalcitonin levels between both groups are highly statistically significant between both groups for any of the items studied in the CSF or blood. However, a wide zone of overlapping values for all items was found between both groups. In Table-2 PCT levels were statistically significantly elevated in patients with bacterial meningitis (mean 4.8 ± 3.85ng/ml) in comparison to PCT levels in patients with non bacterial meningitis were low (mean 0.38±0.25 ng/ml){P< 0.001}. The higher PCT value in patients with non bacterial meningitis is still low compared with the lower value of PCT in patients with bacterial meningitis (range 2.9-11.6 ng/ml and 0.3-0.61ng/ml for bacterial positive and negative meningitis respectively). It is clear from the range of serum procalcitonin level that, there are no overlapping values seen for serum procalcitonin in both groups. The differences in the mean values between both groups are highly statistically significant between both groups for any of the items studied in the CSF or blood. However, a wide zone of overlapping values for all items was found between the bacterial and non bacterial groups. Table-3 shows that there is a positive correlation between serums PCT, TLC and CRP in bacterial positive and negative meningitis but this relation becomes highly significant with bacterial meningitis group. Table-4 shows the sensitivity, specificity, positive predictive value, negative predictive value, the likelihood ratio for positive results (LR+) and the likelihood ratio for negative results (LR-) of serum procalcitonin levels with diagnostic cut off point

Table-4: Performance characteristics of Procalcitonin, total leukocyte count and C-reactive protein.

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
Procalcitonin >0.5 ng/ml	95	94	95	90	17	0.05
TLC <4 or >15 x 109/l	70	66	78	60	3.1	1.04
CRP >10 mg/l	80	90	90	75	8	0.8

PPV=positive predictive value NPV= negative predictive value.
LR+=positive likelihood ratio LH-= negative likelihood ratio.

Table-5: Serum Procalcitonin, total leukocyte count and C-reactive protein level in bacterial meningitis patients on admission, day 3 and day 6.

Test		On admission No = 18	Day 3 No = 15	Day 6 No = 15
Procalcitonin (ng/ml)	Mean ±SD	4.8 ± 3.85	2.31±1.02	0.40 ± 0.21*
	Range	(2.9-11.6)	(1.1–5.6)	(0.3 -0.63)
		p =0.42	P=0.18	p = 0.003
Total Leukocyte count (cell/ml)	Mean ±SD	15,000 ± 2,900	14.2 ± 1,400	12.95 ± 994
	Range	(11,400- 18,600)	(10.1-16.4)	(8.4–13.2)
		p =0.37	p =0.23	p =0.14
C-reactive protein (mg/l)	Mean ±SD	20 ± 6.8	42 ± 22	31 ± 14
	Range	(12.0-56.0)	(18–72)	(14–42)
		p =0.30	P=0.41	p =0.36

* P value <0.001.

> 0.5 ng/ml (95%, 94%, 95%, 90%, 17 and 0.05 respectively) for diagnosis of bacterial meningitis while it was (80%, 90%, 90%, 75%, 8 and 0.8 respectively) for CRP with diagnostic cut off point >10mg/l and for leukocyte count were (70%, 66%, 78%, 60%, 3.1 and 1.04 respectively). Table-5 shows follow up of mean ± SD of serum procalcitonin levels, leukocyte count and CRP levels (on admission, day 3 and day 6) during treatment of 15 patients with bacterial meningitis. A marked statistical significant reduction of procalcitonin levels (mean 0.40±0.2 ng/ml with p< 0.001) was noted on day 6 when compared with mean procalcitonin levels on admission (mean 4.8±3.85 ng/ml). No statistical significant difference with leukocyte count and CRP was seen on follow up.

The remaining 3 bacterial meningitis cases were transferred to government hospital for continuation of management as requested by their parents.

Discussion

A good biomarker for Bacterial infection should fulfill the following criteria; early diagnostic, prognostic value and helpful for therapeutic antimicrobial decisions.[6] 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.[7] 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.[8]

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 4.8ng/ml, and the lower level was 2.9ng/ml, while the higher PCT level in patients with non bacterial meningitis was 0.61ng/ml and the mean was 0.38ng/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 investigators.[9,10] They found that PCT concentration increased in bacterial meningitis with or without shock, but remained low in viral meningitis and inflammatory diseases.

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.[11] 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.[12]

It has been long known that CRP and leukocyte count can differentiate bacterial and non bacterial infection especially meningitis. Our data of a significant difference in the mean CRP and leukocyte count between bacterial and non bacterial meningitis groups, are in agreement with those obtained from many investigators,[10,13] who found that, CRP level and leukocyte count are valuable in distinguishing between bacterial and non bacterial infections. However, initial CRP concentrations can occasionally be low in bacterial positive disease especially in the early stages of the disease it reaches maximum after 24-48 hours and elevated CRP levels have been observed in some cases of non bacterial meningitis.[14] On the other hand, in our study, and study done by Prat et al.,[15] procalcitonin level was not high in cases with non bacterial meningitis. The

level rises dramatically in response to bacterial infection, making it as sensitive and more specific than CRP as a marker of systemic bacterial infection in children. Also, procalcitonin concentrations start to rise from about four hours after single endotoxin challenge, peak at about six hours and remain increased for over twenty four hours.[16-18]

Lacour et al[19] showed that PCT, CRP, and urine dipstick are independent predictors of serious bacterial infection (SBI) in this population of children with fever of unknown origin. They demonstrated that, leucocytosis was not an independent predictor of SBI when PCT, CRP, and urine dipstick have been taken into account. Lacour and his colleagues[19] also developed a scoring system (Laboratory-score) based on the 3 predictive variables independently associated with SBI: PCT, CRP, and urinary dipstick. The principal advantage of the Laboratory-score is its good specificity (81%) for the prediction of SBI associated with the security of a high sensitivity (94%). The good specificity of the Laboratory-score should enable the reliable selection of children who need antibiotic treatment, without over treating those with viral infection.

High PCT levels correlate positively with the severity of the disease, and the presence of multiple organ dysfunction syndrome or shock make it more valuable over serum CRP as a diagnostic and prognostic marker. In the time to come, bedside, rapid, semi-quantitative methods of serum PCT measurements could be more beneficial to the physician when they will be easily accessible.[20,21] Our results disagree with Knudsen et al,[22] who concluded that, PCT and CRP had very high diagnostic accuracy for distinguishing between bacterial and non bacterial infection in patients with spinal fluid pleocytosis. Andreola and his colleagues[23] agreed that CRP and PCT are both valuable markers for detection of severe bacterial infection in children. according to the serum PCT characteristics. It is a more realistic predictor in the early hours of an infection, and if the time needed for its rise in the bloodstream, is considered. It may be a better screening test in emergency settings, because of its better sensitivity and possibility, i.e., lower cost, better availability, and better archival practice.[23]

Our results demonstrated that, Serum procalcitonin with cut off point >0.5 ng/ml showed positive correlation for differentiating acute bacterial meningitis from non bacterial origin than TLC and CRP. It also had a higher sensitivity, specificity, positive predictive value, and negative predictive value. The likelihood ratio for positive results (LR+) and negative results (LR-) for diagnosing bacterial meningitis against CRP and total leukocytic count is better. This is in agreement with many studies.[24,25] Gendrel et al[8] demonstrated that, procalcitonin had better specificity, sensitivity, predictive value and likelihood ratio than CRP, interleukin 6 and interferon-alpha in children for distinguishing between bacterial and viral infections. It also indicates the severity of the bacterial infection and helps to decide antibiotic treatment in the emergency room.

Follow up of our studied cases, showed a significant decrease in procalcitonin levels on day 3 and day 6 after antibiotic treatment. This result is consistent with that obtained by many authors,[3,6,15,24] who found that, serum procalcitonin decreased to a very low, and may to an unidentifiable level with treatment, making it a valuable parameter for evaluating the efficacy of antibiotic treatment and hence diminishing the need for lumbar puncture performed 48-72 hours after admission to assess treatment efficacy.

Potential limitations of our study are that, comparing serum PCT, CRP and TLC in their capacity to distinguish bacterial from non bacterial meningitis has a lot of valuable information but with the major methodological shortcoming of comparing quantitative PCT and TLC results with semi-quantitative CRP results. This suboptimal method may have led to imprecise CRP results. This possibility seems relevant considering that the CRP results on admission in patients with bacterial meningitis are unusually low: mean 20±6.8 mg/L (range 12-56.0 mg/L). Thus the comparison is not fully fair. However, the results are concordant with earlier studies showing results similar to the present one. Based on the results of previous papers and this one, it seems possible that PCT is more accurate than CRP in distinguishing bacterial from non bacterial meningitis. We currently have no data on changes in serum PCT levels occurring among cases with different causative organisms and the question must be asked whether PCT could be reliably used to distinguish between different causative organisms of meningitis or not.

Conclusion

Serum PCT levels can be used in the early diagnosis of acute bacterial meningitis and is more valuable than CRP or TLC. 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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