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Role of Serum Procalcitonin in Monitoring the Response to Treatment of Pediatric Bacterial Meningitis

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ABSTRACT

Background: Early diagnosis and appropriate management are important to reduce the complications of acute bacterial meningitis (ABM). Serum procalcitonin (PCT) is one of the most sensitive and specific markers for identification of ABM. **Objective:** This study was done to evaluate serum PCT as a marker to confirm ABM especially after oral antibiotics intake or when cerebrospinal fluid (CSF) culture is negative and to assess its correlation with outcome of ABM in children. **Methods:** This is a prospective cohort study that included 38 children with suspected ABM who presented to Ain Shams University Children Hospital over a period of 6 months. The PCT levels were measured on admission and 72 hours (h) after treatment. **Results:** Sixteen cases received oral antibiotics before admission, out of which only 6 (38%) patients showed growth in CSF bacterial culture. All the 38 cases showed elevated levels of PCT on admission. There was a significant drop in the mean of PCT level after 72 h of treatment compared to level on admission (7.1±6.5 vs. 11.4±3.7, p=0.001) respectively. There was a significant difference in the mean of PCT level between cases with good versus poor outcome, on admission (7.2±2.8 vs. 13.2±4.4, p<0.001) and 72 h after treatment (4.2±3.5 vs. 12.9±5.3, p<0.001) respectively. **Conclusion:** Serum PCT levels were high in all patients with suspected ABM, including those who received oral antimicrobials for 1-3 days before admission. The decline in PCT levels after treatment was associated with favorable outcome in our cohort.

Keywords: Bacterial meningitis, CSF, Pediatric, Procalcitonin.

INTRODUCTION

Despite effective vaccines, bacterial meningitis remains a major concern in the pediatric age group all throughout the world [(1)]. Low- and middle-income countries (LMICs) have the highest risk of meningitis-related sequelae, with 25% of children who survive meningitis develop complications [(2,3)]. The cornerstones of reducing these problems are early diagnosis and adequate management [(4)]. Acute meningitis in children is still considered a diagnostic dilemma since routine laboratory analysis cannot readily differentiate between septic and aseptic cases [(5)].

Demonstrating the presence of bacteria in cerebrospinal fluid (CSF) samples using CSF cultures is the gold standard in diagnosing acute bacterial meningitis (ABM). CSF cultures can also provide guidance for antibiotic therapy [(6)]. In the acute setting, however, CSF bacterial cultures take too much time to be used in the decision to start proper antimicrobial according to culture and sensitivity [(7)].

A good biomarker for ABM should help with early identification, and assessment of prognosis and should also direct clinicians to make decisions for proper therapeutic strategies [(8)]. Serum procalcitonin (PCT) level was reported to be one of the most effective predictors for discriminating between bacterial and non-bacterial causes of meningitis [(9)].

The aim of this study was to assess the effect of oral antibiotics administration on PCT level and to evaluate serum PCT as a marker to confirm ABM specially when CSF culture is negative and to assess its correlation with outcome of ABM in children.

PATIENTS AND METHODS

This study was conducted among suspected cases of ABM who presented to Ain Shams University Children Hospital over a period of six months. A total of 38 cases of ABM participated in the study.

Inclusion criteria: children from age of 1 month to 15 years of age with suspected ABM.
Exclusion criteria: neonates below 1 month of age, presence of another site of infection in addition to meningitis. Children who had received antimicrobials for more than 3 days prior to admission were excluded.

All relevant demographic information as well as clinical symptoms and signs were recorded on admission and 72 h after treatment, including fever, Glasgow Coma Scale (GCS), frequency of seizures, duration of seizures and feeding tolerance. All the enrolled cases underwent investigations that included total/ differential leukocyte count (TLC), C-reactive protein (CRP), CSF analysis by lumbar puncture. CSF analysis included physical and chemical examinations, cell count and type in addition to direct gram staining and CSF culture. Serum PCT estimation was performed using Human Procalcitonin

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(PCT) ELISA Kit from SinoGeneClon Biotech, HangZhou,Chinawith detection range of 40-800 ng/L.
Meningitis was diagnosed according to history, physical examination, and CSF laboratory findings. ABM was defined if CSF showed bacteria in gram staining and/or culture, cells were predominantly neutrophils, glucose levels were less than two-thirds of blood glucose or CSF protein was elevated (> 45 mg/dl). After 72 hours of treatment, the clinical response and laboratory tests - including TLC, CRP, and serum PCT- were assessed. The prognosis of cases was followed over 14 days.

Ethical considerations:

Informed consent was obtained from the patients' legal guardians before enrollment in the study. Approvals from the Pediatric Department and Ethics Committee, Faculty of medicine, Ain Shams University were obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Data Analysis

Data were analyzed using SPSS 20 statistical software using descriptive and analytic statistics with significance set at 5%. SPSS 22.0 for Windows was used to assemble and analyse the data (SPSS Inc., Chicago, IL, USA). Data were subjected to the Shapiro Walk test in order to see if they were distributed normally. Qualitative data was represented using frequencies and percentages. The variation between quantitative variables in two groups was calculated using the t-test, marginal homogeneity test, McNamar's test and Mann Whitney. If p-value was ≤ 0.05, there is considerable variation for all of our comparisons. To be regarded nonsignificant, p-Values over 0.05 were used to show that the variation was not statistically significant.

RESULTS

Among 38 participants, 17 (44.7%) were males and 21 (55.3%) were females. 13 (34%) had age <1 year, 20 (52.6%) were in the age group 1-5 years and 5 (13%) were in the age group of 6-15 years. The mean age of the participants was 2.7 years (SD=3.4).

The studied population included 22 (58%) children who were presented to our center prior to starting antibiotics and 16 (42%) patients who received oral antimicrobials 1-3 days before presentation. More than 60 % of those who received oral antibiotics showed no growth in CSF culture and sensitivity. Bacterial growth in CSF culture was documented in 19/38 patients. Causative agents included Streptococcus pneumoniae (n = 14), Staphylococcus aureus (n = 2), Haemophilus influenzae (n = 3).

PCT level was elevated in all our patients with suspected ABM. Table 1 summarizes the change in clinical parameters including fever, seizure frequency, feeding tolerance and Glasgow Coma Scale (GCS) on admission, and 72 hours after treatment. A significant improvement of all the parameters were noticed, GCS increased from 11.47±3 on admission, to 13.55±2.59 after treatment.

Table 1 Clinical profile of patients (n = 38) on admission and after 72 hours of treatment

Clinical Characteristics	On admission	After 72 h	p value
Fever			
Min – Max Median (IQR)	38.5- 40.1 39.8(1)	36.6 -39 37(1.2)	<0.001*
Convulsion; n (%)			
No convulsion	6 (15.8)	20 (52.6)	<0.001*
One or more attack	10 (26.3)	16 (42.1)	
Pre-Status epilepticus	22 (57.9)	2 (5.3)	
Feeding tolerance; n (%)			
Poor	36 (95)	10 (26)	<0.001**
Good	2 (5)	28 (74)	
GCS			
Mean ± SD Min – Max	11.47 ± 3 4-15	13.55 ± 2.59 5-15	<0.001***

*Marginal homogeneity test **McNamar's test *** ***Wilcoxon signed-rank test*** GCS = the Glasgow Coma Scale.

Tables 2 and 3 show the laboratory and CSF results of the study cohort. 50% of our cohort showed no growth in CSF culture. There was a significant drop in the mean of serum PCT after 72 hours of treatment compared to serum PCT on admission. This was accompanied by significant drop in TLC, neutrophils count and CRP.

Table 2 Laboratory findings of CSF (n = 38)

Cytology neutrophils count (cells/ microliter) Mean ± SD	9.71±1.63`
Glucose (mg/dl) Mean ± SD	37.42±1.74
Protein (mg /dl) Mean ± SD	116.18±7.85
Culture n (%)	
No growth	19 (50)
Growth	19 (50)

CSF = cerebrospinal fluid

Table 3 Laboratory findings of blood on admission and follow up after 72 hours (n = 38)

	On admission	**After 72 h**	**p value**
	Mean ± SD	**Mean ± SD**	
TLC (/mm3)	15.85±4.01	13.045±4.86	0.001**
Neutrophils %	68.61±8.51	50.39±12.31	0.001*
CRP (mg/dl)	71.6±3.5	46.3±3.6	0.001**
PCT (ng/ml)	11.4 ± 2.7	7.1±1.5	0.001**

*Paired t test ** Wilcoxon signed ranks test
CRP= C- reactive protein, PCT=Procalcitonin, TLC= total leucocytic count.

71 % of our cohort (27/38) recovered with no neurological sequelae or disability, while 8 (21%) patients had neurological sequelae and 3 patients died (8%). A significant difference in the mean of PCT level -72 hours after treatment- was found on comparison between patients with good and poor outcome respectively. A similar difference was noted in the change of median PCT (between admission and 72-hours after treatment) while comparing cases with good vs. poor outcome.

Table 4 Association between procalcitonin and outcome

	PCT on admission		**PCT 72 h after treatment**		**PCT change**	
	Mean ± SD	**Min – Max**	**Mean ± SD**	**Min – Max**	**Median (IQR)**	**Min – Max**
No sequelae (n=27)	7.2±2.8	2.6-13.5	4.2±3.5	0.1-14.3	-3.2 (1.8)	-5.5-1.8
Sequelae (n=11)	13.2±4.4	4.2-19.9	12.9± 5.3	1.7 – 20.5	0.6 (1.2)	-9.5-3.4
Test of significance, p value	Mann Whitney test, p<0.001		Mann Whitney test, p<0.001		Mann Whitney test, p=0.002	

PCT=Procalcitonin

DISCUSSION

Currently, the available diagnostic methods for ABM have serious limitations. The CSF Gram stain can be negative with insufficient organisms in the CSF or after antimicrobial treatment. Cultures often require time for growth and may also be negative in partially treated cases [(10)]. It has been reported that in Egypt, there is widespread misuse of antibiotics [(11)]. Therefore, a diagnostic and therapeutic marker for ABM should be of help in practical setting. The aim of this prospective study was to study the effect of oral antimicrobial administration on PCT level and to assess the role of serum PCT as a diagnostic and therapeutic marker in ABM in the pediatric age group.

The study included 38 patients with suspected ABM, 22/38 patients didn't receive any treatment prior to presentation and 16/38 commenced on antimicrobials before admission. The PCT levels were elevated in all the patients included in our study. This is similar to the results of **Chaudhary *et al.*** who reported that serum PCT levels were significantly high in their cohort, which included 22 patients with ABM, 50% of them had received antibiotics for less than three days prior to admission **(9)**.

The drop in PCT level was significant on third days after antibiotic treatment. This was in agreement with many previous studies that concluded that levels of serum

PCT -after treatment of ABM- showed a significant decline compared to their levels before the start of treatment, making it a valuable marker for diagnosis, and evaluating the appropriateness of antibiotic treatment [12-15].

In their literature review, **Velissaris *et al.*** revised 38 publications and reported that the previously published data agree that, in comparison to other acute phase reactants, serum PCT is superior to diagnose ABM [8].

In our cohort, the level of PCT was an important prognostic factor to predict the outcome of ABM. A significant difference in PCT levels was noted when comparing cases with good versus unfavorable outcome. This agrees with the result of other investigators who found that high values of serum PCT (>7.26 ng/mL) were significant predictor for death in patients with ABM [16]. Similarly, a previous study reported that persistent elevation or further increase in serum PCT levels -48 h after treatment- were associated with poor clinical outcomes [17].

CONCLUSION

Serum PCT levels were high in all patients with suspected ABM, including those who received oral antimicrobials for 1-3 days before admission. The decline in PCT levels after treatment was associated with favorable outcome in our cohort.

REFERENCES

1. **GBD 2016 Neurology Collaborators (2019):** Global, regional, and national burden of neurological disorders, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol., 18(5): 459–480.
2. **Edmond K, Clark A, Korczak V *et al.* (2010):** Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis.,10(5):317–328.
3. **Ramakrishnan M, Ulland A, Steinhardt L *et al.* (2009):** Sequelae due to bacterial meningitis among African children: a systematic literature review. BMC Med., 7(1):47.
4. **Brouwer M, Tunkel A, van de Beek D (2010):** Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev., 23(3):467-492.
5. **Sanaei Dashti A, Alizadeh S, Karimi A *et al.* (2017):** Diagnostic value of lactate, procalcitonin, ferritin, serum-C-reactive protein, and other biomarkers in bacterial and viral meningitis: A cross-sectional study. Medicine (Baltimore), 96(35): e7637.
6. **Ramachandran P, Wilson M (2018):** Diagnostic testing of neurologic infections. Neurol Clin., 36(4):687-703.
7. **Spanos A, Harrell F, Durack D (1989**): Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. JAMA., 262(19):2700-2707.
8. **Velissaris D, Pintea M, Pantzaris N *et al.* (2018):** The role of procalcitonin in the diagnosis of meningitis: A literature review. J Clin Med., 7(6):148.
9. **Chaudhary S, Bhatta N, Lamsal M *et al.* (2018):** Serum procalcitonin in bacterial & non-bacterial meningitis in children. BMC Pediatr., 18(1):342.
10. **Leib S, Boscacci R, Gratzl O, Zimmerli W (1999):** Predictive value of cerebrospinal fluid (CSF) lactate level versus CSF/blood glucose ratio for the diagnosis of bacterial meningitis following neurosurgery. Clin Infect Dis., 29(1):69-74.
11. **Ibrahim O, Saber-Ayad M (2012):** Antibiotics misuse in different hospital wards (a pilot study in an Egyptian hospital). Asian J Pharm Clin Res., 5 (2): 95-97.
12. **Alkholi U, Abd Al-Monem N, Abd El-Azim A, Sultan M (2011):** Serum procalcitonin in viral and bacterial meningitis. J Glob Infect Dis., 3(1):14-18.
13. **Ibrahim K, Abdel-Wahab A, Ibrahim A (2011):** Diagnostic value of serum procalcitonin levels in children with meningitis: a comparison with blood leukocyte count and C-reactive protein. J Pak Med Assoc., 61(4):346-351.
14. **El Shorbagy H, Barseem N, Abdelghani W *et al.* (2018):** The value of serum procalcitonin in acute meningitis in children. J Clin Neurosci., 56:28-33.
15. **Ahmad M, Iqbal J, Ahmad Wani F, Wajid Ali S (2020):** Role of serum procalcitonin in monitoring the response to treatment of pediatric meningitis. *Pediatric Review: International Journal of Pediatric Research*, 7(7), 351-355.
16. **Park B, Kim S, Park S *et al.* (2017):** Procalcitonin as a potential predicting factor for prognosis in bacterial meningitis. J Clin Neurosci., 36:129-133.
17. **Schwarz S, Bertram M, Schwab S *et al.* (2000):** Serum procalcitonin levels in bacterial and abacterial meningitis. Crit Care Med., 28(6):1828-1832.