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A Study of Serum Procalcitonin Level in Hospitalised Pyogenic Bacterial Meningitis Patients

[1.]Dr Sanjeev Kumar, [2.]Dr Rajendra Kumar Kasana, [3.]Dr Rohit Ishran*, [4.] Dr S. Banerjee

[1.]*PG Student, Department of Medicine, S.M.S. Medical College, Jaipur,Rajasthan, India*
[2.]*Assistant Professor, Department of Medicine, S.M.S. Medical College, Jaipur,Rajasthan, India*
[3.]*Assistant Professor*(Corresponding Author) Department of Medicine, S.M.S. Medical College, Jaipur,Rajasthan, India*
[4.] *Senior Professor , Department of Medicine, S.M.S. Medical College, Jaipur,Rajasthan, India*

Abstract
INTRODUCTION
The present study was to pool and analyze the results of all the reported studies to determine the true diagnostic accuracy of PCT in adult patients with suspected meningitis.
AIM AND OBJECTIVE
To predict pyogenic bacterial meningitis on the basis of independent factor like serum procalcitonin against CSF analysis (WBC, biochemistry, CSF culture and gram staining).
METHOD: Observational diagnostic test evaluation study of 64 clinically suspected cases of meningitis had taken consecutively between June 2017-August 2018.
RESULTS: We analysed 64 cases with suspected meningitis where 45 (70.31%) were male; mean age was 42.75±17.47 years. In that 42 patients diagnosed with ABM,13 with TBM and 9 with viral meningitis. In the present study mean for CSF procalcitonin in ABM was 4.87 ± 6.58, in TBM was 0.13±0.17and in viral meningitis was 0.28±0.34. Patients with ABM had raised serum procalcitonin as compared to TBM and viral meningitis. This finding was statistically significant, i.e. P<0.007. Out of 42 ABM patients 37 (88.57%) showed neutrophilic pleocytosis and raised protein in CSF along with raised serum PCT.
Additionally, PCT levels would be expected to decrease in patients receiving antibiotics prior to testing. In our study out of 42 patients of ABM 12 had taken antibiotic and 30 did not taken in previous 72 hrs. In 30 patients those who have not taken antibiotic 27(90%) had raised PCT.
CONCLUSION: Based on the findings of this study it was observed 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.

Keywords
Procalcitonin (PCT);
Acute bacterial meningitis (ABM);
Tubercular meningitis (TBM);
CSF analysis

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I. Introduction

Bacterial meningitis is an acute purulent infection with in the subarachnoid space. It is associated with CNS inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure and stroke.The meninges, subarachnoid space and brain parenchyma all frequently involvedin the inflammatory reaction(meningoencephalitis).

Bacterial meningitis (BM) is a significant cause of morbidity and mortality worldwide, with 1.2 million cases per year, resulting in 135 000 deaths.Due to the high mortality rate and potential neurological sequelae in survivors, there is an urgent need for rapid diagnosis with near 100% sensitivity[1].Early diagnosis and timely initiation of appropriate antibiotic therapy is crucial for reducing mortality from bacterial meningitis[2].Therefore, distinguishing bacterial and other 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.

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[3].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. 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].

CRP has traditionally been used as the biomarker for inflammation. However, CRP may show a delayed increase during the course of bacterial infection, resulting in false-negative tests in the early stages of the disease[5].CRP can also be elevated in viral infections, limiting its ability to discriminate between bacterial and viral aetiologies of meningitis[6].

Procalcitonin (PCT) is now considered to be the best candidate to replace CRP due to its high diagnostic accuracy in various infectious pathologies, including sepsis, acute infectious endocarditis, and pancreatitis[7]. Fibronectin, interleukin 6 (IL-6), and tumour necrosis factor alpha (TNF-α) have also been proposed as potential biomarkers,but have not thus far been accepted widely for clinical use[8].

Normal PCT levels in healthy individuals are <0.1 ng/ml, and levels increase dramatically in response to bacterial infection[9]. It has been hypothesized that this increase is due to the overexpression of the CALC-1 gene and increased release of PCT from various tissues in response to bacterial endotoxins and inflammatory cytokines such as TNF-α, IL-6, and IL-1β[10,11].Unlike CRP, PCT has not been reported to be elevated in viral infections, thus conferring it the important ability to distinguish easily between bacterial and viral aetiologies[12].

II. Material And Method

Study type

Observational diagnostic test evaluation study.

Study Place

Medicine and Neurology Wards, SMS hospital, Jaipur.

Duration of Study

One Year Duration (June 2017-August 2018).

Sample size:

The sample size was 64 clinically suspected meningitis cases at 95% confidence interval and 80% power to verify 94.7% minimum expected accuracy of procalcitonin level.

- Inclusion Criteria:

All patients with clinically suspected meningitis patients admitted in Medicine and Neurology wards SMS Hospital, Jaipur between June 2017 to August 2018.

- Exclusion Criteria:

All clinically suspected cases of meningitis were taken consecutively till sample size achieved.

1. Severely ill patients unable to give consent.
2. Severe localised bacterial infection other than meningitis.
3. Thyroid disorder.
4. Untreated end-stage renal failure.
5. Severe noninfectious inflammatory stimuli (e.g. major burns, severe trauma acute multiorgan failure.

STUDY VARIABLES

We recorded sociodemographic variables (age,sex);

Clinical variables: fever (38˚C), confusion or altered level of consciousness (GCS<15), headache, neck rigidity and sign of meningeal irritation (kernig sign). Additional data included administration of antibiotics treatment in the previous 72 hours. The microbiological studies performed were blood and CSF culture, gram staining, KOH, AFB and polymerase chain reaction amplification of DNA (tubercular and viral). The analytical variables included results from complete blood count, biochemical studies of CSF, and serum PCT.

STATISTICAL ANALYSIS

The data obtained was coded and entered into Microsoft Excel Worksheet. The categorical data was expressed as rates, ratios and proportions. The continuous data was expressed as mean ± standard deviation (SD). The comparison of categorical data was done using Anova test and the comparison of continuous data was done using independent sample 't' test. A probability value ('p' value) of less than or equal to 0.050 at 95% confidence interval was considered as statistically significant.

III. Results

The present study included 64 patients with clinically suspected meningitis where 45 (70.31%) were male; mean age was 42.75±17.45 years. In that 42 patients diagnosed with ABM,13 with TBM and 9 with viral meningitis. ABM diagnosed on the basis of CSF neutrophilic pleocytosis , raised protein, low sugar and culture ,gram stain or blood culture positive. Gram staining positive in 9 patients and one had CSF culture positive for Acinetobacter. CSF PCR positive in 2 cases one for viral (HSV, Entero virus) and one for tubercle bacilli.

Table 1

Patients characteristics	Total no. of cases (n=64)	ABM	TBM	Viral meningitis
Demographic data				
Age	42.75±17.45			
Male	45 (70.31%)	31 (73.81%)	7 (53.85%)	7 (77.78%)
Antibiotics use in previous 72 hrs	17 (26.56%)	12 (28.57%)	3 (23.08%)	2 (22.22%)
Clinical data and symptoms				
Fever (>38˚C)	62 (96.88%)	41 (97.62%)	13 (100%)	8 (88.89%)
Headache	36 (56.25%)	24 (57.14%)	8 (61.54%)	4 (44.44%)
Altered sensorium	62 (96.88%)	41 (97.62%)	12 (92.31%)	9 (100%)
Signs of meningeal irritation	52 (81.25%)	36 (85.71%)	11 (84.62%)	5 (55.56%)

Table 1 displays sociodemographic variables age, sex clinical data, and signs of meningeal irritation as well as comparison between the ABM ,TBM and viral meningitis group.

Regarding clinical presentation fever and headache to altered sensorium. In our study fever was present in 41 (97.62%) and absent in 1(2.38%) patient of ABM. Similarly in TBM all patient 13 (100%) and in Viral out of 9 patients 8 (88.89%) had fever. Similar ratio found in altered sensorium (defined by a Glasgow Coma Scale score below 15). All patients had fever also had altered sensorium. Classic triad present in 30 (46.87%) patients. Other symptoms like headache present in 24 (57.14%) patients ABM, 8(61.54%) patients in TBM and 4 (44.44%) patients in viral. Signs of meningeal irritation in 52 (81.25%) patients and absent in 12 (18.75%). We took those patients who had absent signs of meningeal irritation clinically but had history of other symptoms like headache, fever and altered sensorium. No significant difference were found regarding for fever, headache, altered sensorium, neck rigidity and sign of meningeal irritation.

Table 2

Test	ABM	TBM	Viral meningitis	P- value
WBC (cells/cumm)	691.95 ±929.23	133.85±76.04	445.22±975.89	>0.05
Neutrophils (%)	63.21±26.52	21.25±18.81	22.78±26.68	<0.001
Lymphocyte (%)	34.21±25.85	77.54±19.89	75.33±27.16	<0.001
Protein (mg/dl)	160.05±74.84	134.65±36.23	120.20±44.12	>0.05
Glucose (mg/dl)	26.00±7.03	40.39±22.44	49.33±26.12	<0.001

Table 2 compare cytological and chemical profiles of the CSF from each patient group. CSF examination of the patient groups showed highly significant difference in polymorphs %, lymphocyte %, and CSF glucose (P <0.001). But no significant difference were observed in total CSF WBCs and protein (P >0.05).

Table 3: Mean value for PCT (ng/ml) in meningitis groups

	ABM	TBM	Viral Meningitis	P-value
Mean ±SD	4.87±6.58	0.13±0.17	0.28±0.34	<0.007

Table 3 shows mean serum PCT comparison in ABM, TBM and viral meningitis subgroups. Mean for serum procalcitonin were in ABM 4.87 ± 6.58, TBM 0.13±0.17 and viral meningitis 0.28±0.34. This shows significant difference (P < 0.007). In total ABM patients 37(88.57%) patients had neutrophilic pleocytosis, raised protein in CSF also had raised serum PCT.

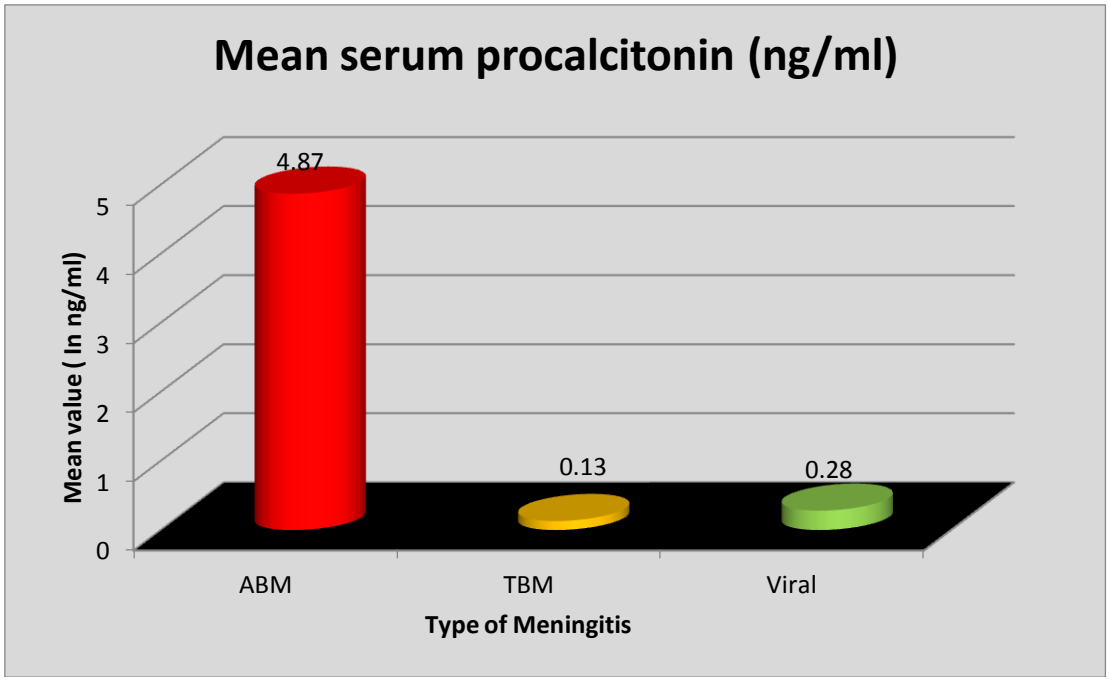

Table 4

Types of meningitis	Antibiotic Taken			Antibiotic Not Taken		
	serum procalcitonin			serum procalcitonin		
	Abnormal	Normal	Total	Abnormal	Normal	Total
ABM	6 (35.29)	6 (35.29)	12 (70.59)	27 (57.45)	3 (6.38)	30 (63.83)
TBM	0 (0.00)	3 (17.65)	3 (17.65)	1 (2.13)	9 (19.15)	10 (21.28)
Viral	0 (0.00)	2 (11.76)	2 (11.76)	1 (2.13)	6 (12.76)	7 (14.89)
Total	6 (35.29)	**11 (64.71)**	**17 (100.00)**	**29 (61.70)**	**18 (38.30)**	**47 (100.00)**

Table 4 shows comparison of serum PCT with antibiotics taken in previous 72 hours or not taken. In the present study out of 42 patients of ABM 12 had taken antibiotic and 30 did not taken in previous 72 hrs. In 30 patients those who have not taken antibiotic 27(90%) had raised PCT and lower level in 6 patients taken antibiotics.

IV. Discussion

It is important to recognise not only bacterial meningitis patients, who need prompt antimicrobial therapy, but also tubercular and viral meningitis patients, who do not need antibiotics. The diagnosis and management of bacterial meningitis require various biological tests and a multidisciplinary approach.

In our study of 64 patients admitted with meningitis male preponderance was noted with 70.31% of patient being male. The male to female ratio was 2.4:1. Similar sex distribution pattern was reported by Erna lund [13]et al where out of 669 patients 397 (59%) were males, 266 (40%) were females and the ratio was 3:2. However, S.P. Dias, M.C. Brouwer[14] found male sex is an independent risk factor for adverse outcome. Females exhibit more robust cell-mediated and humoral immune responses to antigenic challenges, such as infection and vaccination, compared with males, which leads to a lower susceptibility to many infectious diseases.

Incidence of acute bacterial meningitis was more in the age group more than 40 years. Most of the patients were aged above 40 years (64.29%) followed by 20-40 years (30.95%). Mean age for study population was 42.75±12.25 years. Similarly, in a study done on Bacterial Meningitis in the United States, 1998–2007 in adults by Michael C. Thigpen et al[15] in 3188 patients with bacterial meningitis. The median age of patients increased from 30.3 years in 1998–1999 to 41.9 years in 2006–2007 (P<0.001 by the Wilcoxon rank-sum test).

The clinical presentation of meningitis can range from fever and headache to altered sensorium. In our study fever was present in 41 (97.62%) and absent in 1(2.38%) patient of ABM. Similarly in TBM all patient 13 (100%) and in Viral out of 9 patients 8 (88.89%) had fever. In similar study conducted by Diederik van de Beek et al[16] on Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis in 1108 patients. He concluded fever occurred in 77 percent and a change in mental status (defined by a Glasgow Coma Scale score

below 14) in 69 percent. Only 44 percent of episodes were characterized by the classic triad of fever, neck stiffness, and headache.

In our study other symptoms like headache present in 24 (57.14%) patients ABM, 8(61.54%) patients in TBM and 4 (44.44%) patients in viral. Signs of meningeal irritation in 52 (81.25%) patients and absent in 12 (18.75%).Furthermore, the traditionally used meningeal signs, i.e., Kernig's sign, Brudzinski's sign, and nuchal rigidity, have a low diagnostic value[17]. Brouwer et al[18] reported a pooled sensitivity of Kernig's sign in adults to be merely 0.11, while the reported pooled sensitivities of Brudzinski's sign and nuchal rigidity were 0.09 and 0.31, respectively. Due to the low sensitivities of physical signs, it is important to evaluate the entire clinical picture when formulating a differential diagnosis and determining further appropriate diagnostic test.

In the present study no association was observed with CSF total count and type of meningitis i.e. P > 0.05. Our findings were not consistent with a study by Sofia Agueda et al[19] who reported cerebrospinal fluid white blood cell count was significantly higher in patients with bacterial meningitis (mean, 4839 cells/μL) compared to patients with aseptic meningitis (mean, 159 cells/μL, $p < 0.001$).

We also found that mean for CSF neutrophil count in ABM was 63.21±26.52, in TBM was 21.25 ± 18.81 and in viral meningitis was 22.78 ± 26.68.CSF neutrophils significantly higher in ABM as compared to TBM and viral meningitis. Mean for CSF lymphocyte in ABM was 34.21 ± 25.85, in TBM was 77.54 ± 19.89 and in viral meningitis was 75.33 ± 27.16. CSF lymphocyte significantly high in TBM and viral meningitis as compared to ABM. These both finding were significant statistically, P(<0 .001).

These findings were consistent with a study by Venkatesh B et al.[20] WBC count of >500/mm3 with a preponderance of neutrophils in CSF is characteristic of a bacterial meningitis, and a WBC count of >100/mm3 with a preponderance of monocytes is characteristic of a viral meningitis a considerable pattern overlap is often found.

Mean for CSF glucose in ABM was 26.00±7.03, in TBM was 40.39±22.4 and in viral meningitis was 49.33±26.12mg/dl. Patients with meningitis having CSF low glucose in ABM compared to TBM and viral meningitis. This finding was statistically significant, i.e. P < 0.001. In study by Rabab Fouad et al.[21] low CSF glucose level (<45 gm/dL) and CSF/serum glucose ≤0.6 were significantly diagnostic in bacterial meningitis patients.

In the present study we noted that patients with ABM had raised serum procalcitonin as compared to TBM and viral meningitis (i.e. P < 0.007). Our study has remarkable similarities with the one done by Shipra Chaudhary et al[22] in 50 patients, 22 patients fulfilled the criteria for bacterial meningitis and 28 patients non-bacterial meningitis. Serum PCT levels were significantly higher in bacterial meningitis group (median = 2.04 (1.2–3.18) ng/ml) compared to non-bacterial meningitis (median = 0.35 (0.18–0.35) ng/ml); $p < 0.001$.

PCT levels would be expected to decrease in patients receiving antibiotics prior to testing, thus giving misleading results. In our study also PCT level lower side found in those patients who took antibiotics in previous 72 hours. Hu et al[23] found that PCT levels decreased significantly 3 days after the initiation of antibiotic treatment in children with BM. Furthermore, the authors investigated how serum PCT levels correlated to disease severity.[23]

A novel findings from our study is that there are significant high PCT level in patients with CSF neutrophilic pleocytosis and raised protein. No study found that correlate with CSF neutrophil, glucose and protein with procalcitonin. Further study needs for above correlation.

Our study has limitatations including its single centre study design and its small sample size. This sample size was insufficient for some comparisons.our analysis did not include complications (Encephalitis, seizures etc.). Another limitation is the lack of healthy control group,which would have strengthened the study's internal validity. Despite these limitation, we feel that our study reflects the major role of serum PCT in diagnosing ABM and predicting bacteraemia.

V. Conclusion

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.

PCT when used as a supplement to clinical signs and CSF analysis, allows for a more accurate overall diagnosis in patients with suspected meningitis.

The use of PCT serum assays in adult patients with suspected meningitis is therefore recommended, especially when CSF and other reports are awaited, treatment of bacterial meningitis can be started with the use of serum PCT assay thus saving precious time.

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