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Original Research Article

Procalcitonin Levels in Patients with Bacterial Meningitis: A Comparison of Cerebrospinal Fluid and Blood Levels

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Abstract

Background: In developing countries despite advances in antibiotic therapy Bacterial meningitis remains a significant cause of morbidity and mortality. It is commonly diagnosed on basis of clinical presentation and cerebrospinal fluid analysis (CSF). But at times atypical CSF findings are encountered over cases of clinically suspected bacterial meningitis and sometimes due to prior antibiotic use, which puts the treating physician in dilemma regarding initiation of antibiotics. Therefore, an early and a confirmed diagnosis is required for managing such cases and to achieve a favorable outcome. Various studies suggest Procalcitonin to be a promising biomarker for diagnosing bacterial infections. But there are also studies which suggest serum procalcitonin and CSF procalcitonin to be a superior bio-markers in differentiating Bacterial from another non-bacterial meningitis. Therefore, this study is undertaken to find out a biochemical marker to diagnose Bacterial meningitis with increased accuracy which will help the clinicians to differentiate Bacterial meningitis from other common infective meningitis, for proper therapeutic decisions with the following objectives

Aim: A comparative study of cerebrospinal fluid Procalcitonin and serum procalcitonin in patients with bacterial meningitis.

Material and Method: This observational and analytical study was carried out in the Department of General Medicine, among patients admitted under Department of General Medicine and Department of Neurology with a sample size of 60 following inclusion and exclusion criteria. The subjects were evaluated, data collected, blood samples were sent for routine investigations and Lumbar puncture was done in favorable subjects. The CSF analysis was done along with serum and CSF procalcitonin. The test for CSF and Serum procalcitonin were conducted using a Sandwich immunodetection method using ichroma PCT analyzer. The results were analysed using appropriate statistical methods.

Results: In our study it was observed that the elderly age group has a higher association with meningitis. The occurrence of Bacterial meningitis shows a significant seasonal pattern, mostly during winter. Subjects of bacterial meningitis has the longest duration of hospital stay. The predictive value of both serum and CSF procalcitonin are higher in cases of Bacterial meningitis in comparison to non-bacterial meningitis. The ROC analysis concluded that the diagnostic accuracy of CSF procalcitonin is slightly higher but statistically not significant in diagnosing Bacterial meningitis. The Cerebrospinal fluid and Serum procalcitonin were not significant in cases of Viral meningitis and Tubercular meningitis making it a poor biomarker in this meningitis.

Conclusion: Both serum and CSF procalcitonin are better markers in diagnosing Bacterial meningitis and to differentiate them from another non-bacterial meningitis. The study was conducted in context of high morbidity and mortality of Bacterial meningitis and associated complications and the need for a better bio-marker in early diagnosis of Bacterial meningitis and initiation of prompt and proper treatment. The data was analyzed and observations were discussed along with relevant contemporary literature and other studies. Further research works needs to be done on combined use of Serum as well as CSF procalcitonin in cases of Bacterial meningitis.

Keywords: Acid-fast bacilli, cerebrospinal fluid barrier, Procalcitonin and Bacterial Meningitis.

Introduction

Bacterial meningitis is an acute purulent infection within the sub-arachnoid space (SAS). It is associated with a central nervous system (CNS) inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP) and stroke. It is known as 'Meningoencephalitis' when it involves the meninges, SAS and brain parenchyma.[1] It is a life-threatening inflammation of protective membranes (meninges) covering the brain and spinal cord, particularly the arachnoid and the pia mater, associated with the invasion of organisms into the subarachnoid space that can lead to significant long- term sequelae among survivors.[2]

Despite significant progress in reducing the incidence of meningitis, over the past 20 years, there were still an estimated 5 million new cases globally and two lakh ninety thousand deaths from meningitis in the year 2017.[3] The source of infection can be bacterial, viral, fungal or parasitic in origin. Bacterial meningitis (BM) is one among the leading cause of death worldwide from infectious diseases which is responsible for various neurological disability among survivors. The severe after-effects such as hearing loss, visual and physical impairment, cognitive disability, paralysis and seizure disorder has a considerable emotional, social and financial impact on an individual.[4] Again, CSF culture is time consuming which requires two to three days for identifying organisms and the diagnostic yield of CSF gram staining and subsequent culture decreases significantly due to empiric antibiotic treatment prior to hospitalization.[5] Two large studies have reported a decrease in the CSF culture yields from 66% to 62% and 88% to 70% of patients due to prior antimicrobial therapy. Therefore, CSF culture is always not helpful in detecting Bacterial meningitis. [6,7]

Antibiotic use was demonstrated to decrease serum procalcitonin within 24 hours, thus making it inferior in diagnosis of bacterial meningitis.[8] Meta analysis by Wei et al. reveals that both CSF procalcitonin and serum procalcitonin are effective diagnostic for bacterial meningitis but serum procalcitonin is superior to CSF procalcitonin when prior antibiotic use was excluded.[9] There are studies suggesting CSF procalcitonin to be a much better bio-marker for Bacterial meningitis among patients with suspected meningitis with history of empirical antibiotic pretreatment.[10]

Recently serum procalcitonin (PCT) is widely used as a diagnostic biomarker for early diagnosis of sepsis and also to guide antibiotic therapy.[11] Procalcitonin is the

peptide precursor of the hormone calcitonin. It is well-known to be produced by the parafollicular cells of the thyroid, but it is also secreted from neuro endocrine cells of the lung and intestine. The latter two sources of procalcitonin provide its true clinical utility, as they increase its production in response to a pro-inflammatory stimulus, particularly when the stimulus is of bacterial origin.[12] Antibiotic use was demonstrated to decrease serum procalcitonin within 24 hours, thus making it inferior in diagnosis of bacterial meningitis.[8] Meta analysis by Wei et al. reveals that both CSF procalcitonin and serum procalcitonin are effective diagnostic for bacterial meningitis.[9] There are studies suggesting CSF procalcitonin to be a much better bio-marker for Bacterial meningitis among patients with suspected meningitis with history of empirical antibiotic pre-treatment.[10]

With this background of high burden of bacterial meningitis along with rapid deterioration of cases if untreated, with high mortality, prolonged morbidity and irreversible sequelae along with limitation of CSF cytology, biochemical markers and culture in diagnosis of cases early with accuracy, we have taken up this study to evaluate and compare the diagnostic accuracy of CSF and serum procalcitonin in cases of Bacterial meningitis. Further, there is no published literature on diagnostic accuracy of Bacterial meningitis through CSF procalcitonin and serum procalcitonin in Indian context. Therefore, this study will add, more evidence in finding out a new bio-marker for the diagnosis of a fatal disease like bacterial meningitis.

Material and Methods

Study design: Observational and analytical study

Inclusion criteria:

- Age more than 18 years or older
- At least two of the following clinical presentations: Fever, headache, neck stiffness, mental symptoms, consciousness impairment and seizure.
- Receipt of signed and informed consent from the conscious patients or patient attendants

Exclusion criteria:

- Contraindication of lumbar puncture
- Complication with any active malignancy or intracranial space occupying lesion
- Immunocompromised patients

Methodology

All the consecutive cases who were clinically suspected as meningitis, from the Department of General Medicine and Department of Neurology. Patients were screened as per the inclusion criteria and exclusion criteria as mentioned above. Patients were finally included in the study after obtaining a proper written consent regarding the study from the conscious patients or their legal relatives. A proforma was prepared to note the illness in detail. A detail history from the conscious patients or their close relatives were obtained which includes chief complaint, history of present illness, past history, family history, drug history, allergic history and history of any prior antibiotic treatment. Clinical signs and symptoms which are suggestive of meningeal infections like fever, headache, neck stiffness, seizure, vomiting, altered mental status and focal neurological deficit were noted. Past history of chronic diseases like diabetes, tuberculosis, immunodeficient states and others were noted. A proper drug history regarding any prior antibiotic use was also noted. Personal history of smoking, alcohol abuse or any substance abuse if present was elicited.

A thorough General examination and neurological examination was conducted at bedside, and the findings were documented. Fundoscopy was done in all

the cases and the findings were noted. Lumbar Puncture was done only after excluding the contraindications. All the cases where the Lumbar Puncture couldn't be performed were excluded from the study.

Investigations and procedures

Routine laboratory investigations like complete blood count, fasting blood sugar, renal function test, liver function test, serum electrolytes like sodium and potassium, urine routine and microscopy and ECG were done. Chest X ray was done to rule out any infective pathology like pneumonia or Koch. Other relevant investigations needed were also done. Appropriate treatment was started as per the experienced unit wise treating physician.

Lumbar puncture:

Patients were positioned in the lateral decubitus position, with the vertebral line in horizontal plane, head in neural position and knees flexed properly. Maintaining proper aseptic procedures like application of no-touch technique, sterile drapes and after cleaning the area with povidine iodine were done. With the help of a spinal needle of size 20 or 22 gauze, a lumbar puncture was done after identifying the L3-L4 space by the help of iliac crest. After the needle enters the proper subarachnoid space, and the cerebrospinal fluid comes out, the opening pressure was noted. Adequate sample of CSF fluid was drawn and was sent for cell count, cytology, protein, glucose, gram stain, culture, AFB staining, CBNAAT, different PCR for viral etiologies like HSV1 and2, India ink and Cerebrospinal fluid procalcitonin. A blood sample for serum procalcitonin was also obtained simultaneously. CT scans or MRI brain if needed or indicated by clinical scenario was done to note the meningeal enhancement and to evaluate for any complications associated.

Statistical analyses:

Categorical variable like age group, gender, fever, vomiting, headache, altered sensorium, seizure, neck stiffness, gram staining, CSF culture, AFB, CBNAAT, Type of meningitis based upon CSF, seasonal variation, organism for bacterial culture and comorbidities was studied by frequency procedure. Comparison of scale variables like, CSF procalcitonin, serum procalcitonin, TLC, protein, glucose, ADA by type of meningitis based upon CSF was done by using one way ANOVA analysis. Receiver operating characteristics (ROC) was done to evaluate CSF procalcitonin and serum procalcitonin as a good marker of bacterial meningitis.

Result

Table 1: Comparison of CSF procalcitonin, Serum procalcitonin and TLC with Type of Meningitis

Variable	Bacterial Mean ±SD	TB Mean ±SD	Viral Mean ±SD
CSF Procalcitonin ng/ml	1.8 ±1.2	0.12± 0.03	0.20 ±0.53
Serum Procalcitonin ng/ml	2.6± 2.1	0.39 ±0.11	0.54± 92.03
TLC cells/microliter	1371.1 ±2026.2	4001.1 ±1542.3	5342.03 ±2243.11

Furnished comparison of mean CSF procalcitonin, serum procalcitonin and TLC with type of meningitis. The mean CSF procalcitonin for bacterial meningitis was significantly higher than that of the TB meningitis and viral meningitis cases. The mean serum procalcitonin for bacterial meningitis was significantly higher than that of the TB meningitis and viral meningitis cases. The mean TLC for bacterial meningitis was significantly higher than that of the TB meningitis and viral meningitis cases.

Table 2: Comparison of Protein, Glucose and ADA with type of meningitis.

Variable	Bacterial Mean ±SD	TB Mean ±SD	Viral Mean ±SD
Protein in mg/dl	201.2± 110.4	215.1 ±63.5	122.5± 105.2
Glucose in mg/dl	21.6 ±7.2	30.4 ±5.0	42.1± 10.3
ADA in U/L	1.4 ±1.5	10.4 ±3.2	18.2± 2.1

The difference in the mean protein level was found significant. The mean protein level for bacterial meningitis cases was the highest and that for viral meningitis was the lowest. The difference in the mean glucose level was found significant. The mean glucose level for viral meningitis cases was the highest and that for bacterial meningitis was the lowest. The difference in the mean ADA level was found significant. The mean ADA level for TB meningitis cases was the highest and that for bacterial meningitis was the lowest.

Discussion

Bacterial meningitis being a medical emergency requires a prompt therapy to prevent mortality and disability among survivors.[13] Various intracranial complications like cerebral herniation due to brain edema and hydrocephalus, thrombosis of cerebral veins and sinuses secondary to mastoiditis, seizures, cerebritis, brain abscess and cerebrovascular accidents like stroke and hemorrhage can be sometimes life threatening or a troublesome long-term sequel.[14] When managing a case of meningitis, an early diagnosis along with an etiology is required for early initiation of proper treatment which has a greater impact on the clinical course as well as outcome of the disease. In a developing country like India where most of the cases of meningitis presents with prior antibiotic use, which can alter the CSF picture as a result keeps the treating physician in dilemma regarding the diagnosis as well as the treatment. This study was carried out to evaluate the efficacy of CSF procalcitonin and Serum procalcitonin as markers of bacterial meningitis which may help the clinician to differentiate bacterial meningitis from other etiology of meningitis like tubercular or viral meningitis.

Makoo et al. 2010 [15] in their prospective cross-sectional study of 100 patients of meningitis had a mean age of 46.32 ±22.008 years which is comparable to our study. The study by Makoo et al.2010 and our study have almost equal male to female ratio while in a similar study by Li et al. 2017 [10] has a significant male preponderance. Comparable demographic profile in various studies implied that Meningitis did not have any gender association. Relatively higher mean age of the Meningitis patients in studies makes an association with elderly population.

Li et al. 2017 [10] has also compared the mean protein levels in different meningitis. He found that the mean protein level in bacterial and tubercular meningitis were in higher zone while for viral meningitis was the least. Various similar studies like Li et al. 2017 [10] and Makoo et al. 2010 [15] have also compared mean protein level among different meningitis cases, and they found that the viral meningitis possess the highest mean protein level among all meningitides. Another similar study like Shen et al. 2015 [16] in his retrospective study of 178 patients on different meningitis has compared the mean leukocyte count in blood. Where he found that cases with Bacterial meningitis have a high leukocyte count in blood 3800*10 6 /L while in non-bacterial meningitis the leukocyte count was significantly low 280 *10 6 /L.

Konstantinidis et al. 2014 [17] in their prospective study from Department of Internal Medicine on 58 cases of meningitis found that the mean CSF

procalcitonin level in cases of bacterial meningitis were 4.714 ± 1.59 ng/ml and the mean CSFP CT level in cases of viral meningitis were 0.1327 ± 0.03 ng/ml. Another similar study by Shen et al. [16] has also compared the median serum and CSF procalcitonin concentration in cases of bacterial and non-bacterial meningitis. The median serum concentration of PCT in the BM and non-BM patients was 4.22ng/mL and 0.41 ng/mL, respectively. In addition, the CSF PCT concentration in the BM and non-BM patients was 1.88 ng/mL and 0.34 ng/mL, respectively, which indicates that both serum and CSF procalcitonin are a good marker for bacterial meningitis in comparison to non-bacterial meningitis.

Vikse et al. 2017 [12] in 2015, conducted a meta- analysis on the diagnostic accuracy of Serum PCT in BM in adults. After pooling 9 studies, they found that Serum PCT is a highly accurate test for diagnosing meningitis. The pooled sensitivity and specificity were 90% and 98% respectively. They also found that PCT is superior to CRP levels. Wei et al. 2016 [9] and colleagues published a meta-analysis, which focused on the role of diagnostic accuracy of procalcitonin levels in blood and CSF in cases of Bacterial meningitis. This meta-analysis concluded that both CSF and blood PCT are efficient in diagnosing Bacterial meningitis but blood PCT exhibits a superior role in establishing BM.

Conclusion

The study was conducted in context of high morbidity and mortality of Bacterial meningitis and associated complications and the need for a better bio- marker in early diagnosis of Bacterial meningitis and initiation of prompt and proper treatment. The data was analyzed and observations were discussed along with relevant contemporary literature and other studies.

References

1. Jameson et al. Harrison's Principles of Internal Medicine. 20th edition. McGraw-Hill: 2018.133: Acute Meningitis; page 998.
2. Hoffman O, Weber J. Review: Pathophysiology and treatment of bacterial meningitis. Therapeutic Advances in Neurological Disorders. 2009;2(6):401- 412.
3. Defeating meningitis 2030: baseline situation analysis [Internet]. Who. int. 2020.
4. Zunt J, Kassebaum N, Blake N, Glennie L, Wright C, Nichols E et al. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2018;17(12):1061-1082.
5. Alons I, Verheul R, Kuipers I, Jellema K, Wermer M, Algra Aet al. Procalcitonin in cerebrospinal fluid in meningitis: a prospective diagnostic study. Brain and Behavior. 2016;6(11):00545.
6. Bohr V, Rasmussen N, Hansen B, Kjersem H, Jessen O, Johnsen Net al. 875Cases of bacterial meningitis: Diagnostic procedures and the impact of preadmission antibiotic therapy Part III of a three-part series. Journal of Infection. 1983;7(3):193-202.
7. Nigrovic LE, Malley R, Macias CG, Kanegaye JT, Moro-Sutherland DM, Schremmer RD, Schwab SH, Agrawal D, Mansour KM, Bennett JE: Effect of antibiotic pre-treatment on cerebrospinal fluid profiles of children with bacterial meningitis. Pediatrics. 2008; 122(4):726-730.
8. Viallon A, Guyomarc'h P, Guyomarc'h S, Tardy B, Robert F, Marjollet O et al. Critical Care. 2005;9(4):344.
9. Wei T, Hu Z, Qin B, Ma N, Tang Q, Wang L et al. Diagnostic Accuracy of Procalcitonin in Bacterial Meningitis

Versus Nonbacterial Meningitis. Medicine. 2016;95(11):3079
10. Li W, Sun X, Yuan F, Gao Q, Ma Y, Jiang Y et al. Diagnostic Accuracy of Cerebrospinal Fluid Procalcitonin in Bacterial Meningitis Patients with Empiric Antibiotic Pre-treatment. Journal of Clinical Microbiology. 2017;55(4):1193-1204.
11. Vijayan A, Vanimaya, Ravindran S, Saikant R, Lakshmi S, Kartik Ret al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. Journal of Intensive Care. 2017;5(1).
12. Taylor R, Jones A, Kelly S, Simpson M, Mabey J. A Review of the Value of Procalcitonin as a Marker of Infection. Cureus. 2017.
13. N, Thomas M. Meningitis in adults: diagnosis and management. Internal Medicine Journal. 2018;48(11):1294-1307.
14. Silvia Schonenberger C. Complications of Adult Bacterial Meningitis and their Neurocritical Care Management? A Case Report and Short Review. Journal of Neuroinfectious Diseases. 2015;06(02).
15. Makoo. Diagnostic Value of Serum and Serum and Cerebrospinal Fluid Procalcitonin in Differentiation Bacterial from Aseptic Meningitis. American Journal of Infectious Diseases. 2010;6(4):93-97.
16. Shen H, Gao W, Cheng J, Zhao S, Sun Y, Han Z et al. Direct comparison of the diagnostic accuracy between blood and cerebrospinal fluid procalcitonin levels in patients with meningitis. Clinical Biochemistry. 2015;48(16-17):1079-1082.
17. Konstantinidis T, Cassimos D, Gioka T, Tsigalou C, Parasidis T, Alexandropoulou I et al. Can Procalcitonin in Cerebrospinal Fluid be a Diagnostic Tool for Meningitis? Journal of Clinical Laboratory Analysis. 2014;29(3):169-174.