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Original Research Article

Role of procalcitonin in viral and bacterial meningitis

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ABSTRACT

Background: Meningitis is one of the most common central nervous system infections by bacteria, virus or fungus encountered in infants and children. Early diagnosis of meningitis and differentiation of bacterial from non-bacterial/ viral meningitis tends to play an important role in the emergency management of children with suspected meningitis. While cerebrospinal fluid analysis is popular, along with biomarkers: C-reactive protein and white blood cell count, serum procalcitonin seems to offer an even better specificity.
Methods: A hospital based cross-sectional-study was conducted in department of neurology in collaboration with department of pathology, Medanta, Medicity, Gurugram, for a period of one year from March 2018 to 2019. 100 children aged 4 months to 12 years, with suspected meningitis were enrolled. The study group was further subdivided into two groups, based upon their bacteriological profile: bacterial meningitis and viral meningitis.
Results: For both the groups, the common clinical presentations were fever (100% and 96.88%), convulsions (58.33% and 45.31%), vomiting (25% and 43.75%), The demographic and clinical profile of the 2 groups was largely comparable. Serum PCT levels were significantly higher in bacterial meningitis group compared to non-bacterial meningitis with $p<0.001$. The sensitivity of serum PCT was found to be 97% and superior to CRP in terms of accuracy in identification and to assess the severity. Procalcitonin is an ideal marker with highest accuracy for bacterial infections.
Conclusions: Serum PCT can act as a more sensitive and specific diagnostic tool in early differentiation of bacterial from non-bacterial meningitis in children.

Keywords: Meningitis, Procalcitonin, Cerebrospinal fluid, C-reactive protein

INTRODUCTION

Meningitis is one of the most common central nervous system infections by bacteria, virus or fungus or sometimes parasitic in origin, which may be encountered in infants and children.[1] Despite the advances in diagnosis and treatment of infectious diseases, meningitis and encephalitis are still considered as important cause of mortality and morbidity. Cerebrospinal fluid (CSF) analysis is a known and popular standard for diagnosing bacterial meningitis, along with biomarkers like C-reactive protein and white blood cell count.[2] 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 and identifying the frequently encountered viral agents via polymerase chain reactions 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. After intensive research for new and rapid diagnostic methods for differential diagnosis of meningitis, serum procalcitonin has been found to be the best marker for diagnosis of sepsis and shows relation with the severity of microbial invasion, as well as the extent of disease.[3] Practitioners now consider procalcitonin (PCT) as more useful and superior,

clinically, to C-reactive Protein (CRP) due to its diagnostic accuracy in infectious pathologies, sepsis, acute infectious endocarditis, and pancreatitis.[4,5] Studies have also shown PCT as powerful diagnostic test for the assessment of suspected meningitis, allowing rapid differentiation between bacterial and non-bacterial aetiologies, and earlier initiation of appropriate and necessary therapies. The evidence suggests that while serum PCT offers a similar or even better specificity to the traditionally used CSF markers of meningitis, it also confers a higher sensitivity allowing for more accurate overall diagnosis in patients with suspected meningitis. Although PCT serum assays has been recommended in adult patients with suspected meningitis but not in children.[6] Therefore the present study was planned so as to measure the levels serum PCT level, TLC and CSF among meningitis patients and aims to analyze its role as a marker to differentiate bacterial and viral meningitis and possible replacement to current practice of testing C-reactive protein.

METHODS

This hospital based observational-cross-sectional-study was conducted in department of neurology in collaboration with department of pathology, Medanta, Medicity, Gurugram, for a period of one year from March 2018-2019. Ethical clearance was obtained from Institutional Ethical Committee. 100 children aged 4 months to 12 years admitted during the study period with suspected meningitis were enrolled. Simple ramdon sampling technique was used to select and enroll all the 100 cases. Written and informed consent was obtained from their parents. Patients not giving consent, or less than 4 months of age, or more than 12 years of age, or having secondary site of infection apart from meningitis, or having received antibiotics for more than 3 days prior to admission, were excluded. Relevant diagnostic investigations were carried out on the patients, like total/differential leukocyte count, CSF analysis by lumbar puncture. 2ml of blood was taken from anterior cubital vein for serum PCT estimation which as performed on the fully-auto chemiluminescence immunoassay analyzer (CLIA).

Meningitis was diagnosed mainly by evaluating the history and by physical examination. CSF laboratory findings, identification of bacterial agents in gram staining, and glucose levels less than two-third of blood glucose or elevated CSF protein (>45 mg/dl) after receiving antibiotics for three days, also supported the diagnosis. Meningitis was reported when there was no growth of microorganism, had lymphocyte count predominantly, and had normal (15-45 mg/dl) or slightly increased (up to 60 mg/dl) protein. The study group was further subdivided into two groups, bases upon their bacteriological profile: group 'B' with bacterial meningitis and group 'V' with viral meningitis. Detailed demographic/clinical profile as well as laboratory parameters and investigations were carried out as per designed proforma. Data were analyzed using latest SPSS statistical software as well as Microsoft Excel sheets and performing analytic statistics like chi-square tests, independent sample 't' test and by analyzing p value, with $p<0.05$ considered significant.

RESULTS

Amongst the 100 patients enrolled, 36 patients fulfilled the criteria for bacterial meningitis and 64 patients for viral meningitis. The median age of the studied population in group 'B' was 24 months with 52.78% being males. The respective data for group 'V' was 27.5 months with 54.69% being males. For both the groups with bacterial and viral meningitis, the common clinical presentations were fever (100% and 96.88%), convulsions (58.33% and 45.31%), vomiting (25% and 43.75%), neck stiffness (44.44% and 18.75%), decreased feeding among infants (33.33% and 23.44%) and raised intracranial pressure (22.22% and 14.06%). The demographic and clinical profile of the 2 groups was largely comparable with no statistically significant difference (Table 1).

Table 1: Demographic and clinical profile of patients.

Characteristics	Group 'B': bacterial meningitis (N=36)	%	Group 'V': viral meningitis (N=64)	%	P value
Median age (Months)	24		27.5		>0.05
Gender: Male	19	52.78	35	54.69	>0.05
Gender: Female	17	47.22	29	45.31	
Illness duration	4.25±2.25		5.00±2.75		
≤3 days	12	33.33	6	9.38	<0.05*
>3 days	24	66.67	58	90.63	<0.05*
Fever	36	100.00	62	96.88	>0.05
Convulsions	21	58.33	29	45.31	>0.05
Vomiting	9	25.00	28	43.75	>0.05
Headache	6	16.67	16	25.00	>0.05

Continued.

Characteristics	Group 'B': bacterial meningitis (N=36)	%	Group 'V': viral meningitis (N=64)	%	P value
Neck pain	13	36.11	2	3.13	<0.05*
Neck stiffness	16	44.44	12	18.75	>0.05
Loss of consciousness	8	22.22	4	6.25	<0.05*
Excessive crying	5	13.89	7	10.94	>0.05
Decreased feeding	12	33.33	15	23.44	>0.05
Kernig's Sign	2	5.56	3	4.69	>0.05
Brudzinski sign	1	2.78	5	7.81	<0.05*
Raised Intracranial pressure	8	22.22	9	14.06	>0.05
ICU need	7	19.44	11	17.19	>0.05
Mechanical ventilation	3	8.33	10	15.63	>0.05

*p<0.05 was considered significant

Table 2: Lab findings of blood and cerebrospinal fluid (CSF).

Lab parameter	Group 'B': bacterial meningitis (N=36)	Group 'V': viral meningitis (N=64)	P value
Serum procalcitonin (PCT) (ng/ml)	2.74±2.32	0.45±0.20	< 0.001**
Total leukocyte count (TLC): cells per cubic millimeter	14,056±7885	8724±3645	<0.05*
Neutrophil (%)	58.93±18.66	42.46±15.82	>0.05
CSF			
TLC (/mm^3)	18.23±7.44	10.25±6.92	>0.05
Neutrophil (%)	29.56±20.59	23.48±16.09	>0.05
Glucose (% of blood glucose)	44.06±10.95	39.33±10.84	>0.05
Protein (mg/dl)	70.47±45.00	44.71±16.17	<0.05*

*p<0.05 was considered significant; **p<0.001 was considered highly significant

Table 3: Efficacy of serum PCT, TLC and CSF cytochemistry in diagnosis of bacterial meningitis.

Test	Sensitivity (%)	Specificity (%)	P value
Serum PCT	97.00	84.00	< 0.001
TLC	82.00	55.00	-
CSF			
TLC	49.00	63.00	-
Neutrophil	26.00	83.00	-
Glucose	87.00	14.00	-
Protein	71.00	60.00	-

Serum PCT levels were significantly higher in bacterial meningitis group compared to non-bacterial meningitis with p<0.001. Total leukocyte count was found significantly deranged in group 'B', while it was within the range for group 'V'. The protein levels for cerebrospinal fluids were found deranged and significantly higher in group B (70.47±45.00 mg/dl). Procalcitonin thus showed greater significance in bacterial meningitis, when compared to the results of total leukocyte or WBC cells per cubic millimeter count or CSF cytochemistry, in terms of TLC, Glucose and Neutrophil (Table 2).

The sensitivity of serum PCT and TLC was found to be 97% (81-98) and 82% (66-91) respectively. The specificity of serum PCT and TLC was also found to be 84% and 55% respectively. The sensitivity and specificity of CSF was also not much as compared, except for CSF protein (>45 mg/dl) for diagnosis of bacterial meningitis (Table 3).

DISCUSSION

Among healthy individuals, circulating levels of PCT are very low (≤0.01 ng/ml). In viral infection and inflammation, there can be a slight increase but rarely above 1.0 ng/ml.[7] Gendrel et al.[8] has demonstrated elevated PCT levels in bacterial meningitis and Ibrahim et al demonstrated cut off point >0.5 ng/ml showing positive correlation for differentiating acute bacterial meningitis from non-bacterial origin.[9] In the current study, thirty-six children had presentation of bacterial meningitis out of which 16 had received antibiotics for 1-3 days prior to admission.

Their clinical findings included CSF features like leukocytosis with neutrophilic predominance, decreased glucose and/or elevated protein. Leukocyte count is known to differentiate bacterial and non-bacterial

infection including meningitis.[10,11] Our study showed that TLC was significantly higher in bacterial meningitis but CSF parameters apart from protein had no significant difference between the two groups. Assicot et al first proposed serum PCT as an early marker of bacteremia in 1993, since then; there have been various descriptive reports on PCT.[12] Early diagnosis of meningitis and differentiation of bacterial from non-bacterial/viral meningitis tends to play an important role in the emergency management of children with suspected meningitis. In the present study, procalcitonin has shown greater significance in bacterial meningitis than total leukocyte count or CSF.

That way the area under receiver operating characteristics (ROC) curve was maximum for procalcitonin when compared to total leukocyte count and CSF cytochemistry, similar results were obtained by Chaudhary et al in 2018.[13] Procalcitonin has been found to be quite specific and sensitive marker of infections of respiratory tract and others like: meningitis, acute infectious endocarditis and pancreatitis.[5] Role of serum PCT in bacterial meningitis can be explained by the increase of calcitonin gene (CALC-I gene) expression and release of PCT from all parenchymal tissues in presence of bacterial lipopolysaccharides and cytokines, already associated with severe bacterial infections.[14]

In current study, the sensitivity and specificity of PCT was similar to the one pointed by Alkholi et al,[15] showing that PCT concentration > 2 ng/ml had 100% sensitivity and negative predictive value but only 66% specificity and 68% positive predictive value for bacterial meningitis. In several other studies from various parts of the world too, procalcitonin has been found to have better specificity, sensitivity, predictive value and likelihood ratio than CRP, interleukin 6 and interferon-alpha in children for distinguishing between bacterial and viral infections.[6,8,9,11] As found by Nargis et al current study has also suggests PCT to be superior to CRP in terms of accuracy in identification and to assess the severity of sepsis, however, both markers cannot differentiate infectious from noninfectious clinical syndrome.[16] But, procalcitonin is an ideal marker with highest accuracy for bacterial infections, allowing an early diagnosis, informing about the course and prognosis of the disease and facilitating therapeutic decisions.[17-19]

Limitations

Although studies conducted within and outside India have shown decrease of PCT by way of antibiotics treatment, lack of prevalent knowledge about this among the diagnostic community and high cost of procalcitonin kit, leading to lower follow-up and inadequate documentation and treatment evaluation, can be considered as a big limitation of the present study.

CONCLUSION

Early diagnosis of bacterial meningitis among children can be possible by evaluating serum PCT. It can help in differentiating bacterial and non-bacterial meningitis for early management of disease. Thus, serum PCT can act as a more sensitive and specific diagnostic tool in early differentiation of bacterial from non-bacterial meningitis in children and more such studies are needed to establish better standards in meningitis disease diagnose and control.

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