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RAISED ADENOSINE DEAMINASE AND C-REACTIVE PROTEIN IN CEREBROSPINAL FLUID: A DIAGNOSTIC MARKER OF TUBERCULOUS AND BACTERIAL MENINGITIS

General Medicine

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ABSTRACT

Objective: To establish diagnostic role of CSF C-reactive protein (CRP) and Adenosine deaminase(ADA) quantitatively in meningitis.
Method: This prospective study was done on108 patients. According to serum & CSF analysis 36 cases had pyogenic meningitis, 30 case had tuberculous meningitis and 42 cases had aseptic meningitis. Along with other appropriate investigations,quantitative CSF - CRP and CSF-ADA was assayed and data were analysed to set a diagnostic level and sensitivity and specificity of CSF –CRP and CSF-ADA in meningitis.
Result:The differences in the mean values were statistically significant for CSF protein levels, CSF leukocyte count, and CSF/serum glucose between bacterial and aseptic meningitis groups ($p<0.001$). Values of CSF CRP and CSF ADA had significant difference in different meningitis group ($p<0.001$).
Conclusion:CSF CRP and CSF ADA can easily differentiate bacterial and tuberculous meningitis from other types of meningitis with great sensitivity and specificity .

KEYWORDS

CSF C-reactive protein(CRP),CSF-Adenosine deaminase(ADA),Meningitis.

BACKGROUND

Meningitis, one of the dreaded infection of the central nervous system, can be caused by bacteria including tubercle bacilli, virus and rarely by fungus. If not treated promptly & properly, meningitis can lead to irreversible neurological impairment & even death also. Etiological diagnosis is necessary as treatment protocol is different for bacterial, tubercular, and non-bacterial meningitis. Besides biochemical and cytological examination , special, cost effective, but reliable and rapid tests are necessary for differentiation of various types of meningitis. CSF CRP & CSF ADA can be used as rapid test in identifying bacterial and tubercular meningitis respectively.The level of both ADA and CRP are low in cases of viral meningitis.

C-Reactive protein an "acute phase reactant" and a sensitive marker of inflammation is secreted from the liver in response to inflammation. CSF CRP level should be high in meningitis due to passive diffusion across the highly inflamed meninges[1]. CSF CRP can be helpful in rapid diagnosis of pyogenic meningitis which has been evaluated by various studies.

Isolation of mycobacterium tuberculosis from CSF samples takes time and inappropriate to help in clinical judgement with respect to treatment. Detection of acid fast bacilli from CSF smear is poorly sensitive. Detection of Mycobacterium tuberculosis specific DNA by PCR is not available in all centers. An enzyme of purine catabolism, Adenosine deaminase (ADA), levels remain high in fluid of tuberculous pleural and peritoneal effusion. High ADA levels in tuberculosis appear to be related to the subset of activated T-lymphocytes in response to tuberculous antigens[2]. Thus this study was performed to evaluate the utility of CSF CRP & CSF ADA in specific diagnosis of meningitis.

OBJECTIVE:

To evaluate diagnostic utility of CSF CRP & CSF ADA in meningitis in adults.

MATERIALS AND METHODS

A total of 108 clinically suspected cases of meningitis, admitted in Burdwan Medical College & Hospital, Burdwan were studied.

All patients with fever, headache and signs of meningeal irritation with or without altered sensorium were put to CSF study. Those conforming to either tubercular, bacterial or aseptic meningitis group (as described later on) were included in the analysis.

History and clinical findings of all the patients were recorded in a proforma.

In the first 24 hours of hospitalization, all cases underwent lumbar puncture and CSF samples were collected. CSF was then sent for ADA and CRP estimation, cytology, biochemistry, bacteriology, culture and sensitivity. CSF CRP was determined by simple antigen antibody precipitation test, *i.e.,* latex slide agglutination method with the help of commercially available kit. Presence of agglutination indicates CSF-CRP concentration of more than 6 µg/mland was considered positive.

- CSF-ADA activity was estimated in all 108 cases spectrophotometrically by Guisti[3] method and comparison was made between the levels in tuberculous meningitis, pyogenic meningitis,and aseptic meningitis.

Of the selected 108 cases, 30 cases were of tuberculous meningitis , 36 cases of pyogenic meningitis and 42 cases of aseptic meningitis.

The valid set of criteria,as used by Ahuja et al[4] was used to categorize tuberculous meningitis patients. The criteria was as follows:

A) Clinical features:
- Fever and headache more than 14 days (mandatory)
- Vomiting, alteration of sensorium, focal deficits (optional).

B) CSF showing:
- Pleocytosis with more than 20 cells
- More than 60% lymphocytes
- Sugar less than 60 percent of corresponding blood sugar
- Negative Indian ink preparation studies
- Malignant cytology (when relevant)

C) CT showing one or more of
- Exudates in basal cistern
- Hydrocephalus
- Infarcts
- Gyral enhancement

D) Active extraneural tuberculosis as evidenced by appropriate
- Radiological tests
- Microbiological tests or
- Ceseation necrosis on histopathological examination.

Diagnostic criteria of pyogenic meningitis: The typical CSF findings were elevated pressure, neutrophilic pleocytosis ,i.e. cell count >100 WBC/cu.mm consisting of more than 90% polymorphs, elevated protein >40 mg%, sugar ≤50 % of the blood sugar ,cloudy or turbid appearance, culture and gram staining may be positive for bacteria.

Diagnostic criteria of Aseptic meningitis: The typical findings were: sugar ≤ 2/3 of blood sugar, protein s ≤ 40 mg %,cell count > 100 WBC/cu.mm and consisted predominantly of lymphocytes.

Statistical Analysis was done using statistics software IBM SPSS version 23.The tests used were Wilcoxon Rank sum Test, Mann-Whitney Test, Pearson Correlation and Chi-square test.

RESULTS

During the study period a total of 108 patients were enrolled in this study after obtaining the informed written consent. The age of the patients in this study ranged from 13 years to 62 years. The mean ± SD age of the patients was 29.8 ± 11.75 years with highest number of patients (30%) was observed in the age group of 21 to 30 years. There were 73 males and 35 females with a male:female ratio of 2.1:1 .

According to serum & CSF analysis 30 cases were of tuberculous meningitis , 36 cases of pyogenic meningitis and 42 cases of aseptic meningitis .

Mean CSF ADA levels in tuberculous meningitis groups was significantly higher as compared to pyogenic meningitis and viral meningitis (Table 1).

Table 1 : CSF ADA value in different groups

ADA (P< 0.05)	TUBERCULAR MENINGITIS	BACTERIAL MENINGITIS	VIRAL MENINGITIS
No. of cases	30	36	42
Mean	15.0567	6.6875	4.6710
Median	14.6500	6.6500	4.9500
Std. Deviation	4.91666	1.28668	1.03577
Minimum	9.20	4.60	2.80
Maximum	36.50	8.40	6.10

There was no correlation between CSF sugar levels with ADA in cases of TB meningitis (Table 2).

Table-2: CSF ADA levels in TB meningitis in relation to CSF sugar

CSF sugar (mg%)	No. of cases	CSF ADA Levels (U/L)		
		Mean	SD	Range
Less than 40	25	15.29	1.97	9.2-36
More than 40	5	13.7	2.05	11.-18.50

The mean values and ranges for CSF and serum markers in bacterial and aseptic meningitis groups are shown in table 3. The differences in the mean values were statistically significant for CSF protein levels, CSF leukocyte count, and CSF/serum glucose between bacterial and aseptic meningitis groups (p<0.001). Values of serum CRP had significant difference in bacterial meningitis group compared to other group (p<0.001).

Table 3:

Variables		Bacterial meningitis group (n=36)	Aseptic meningitis group (n=42)
Serum glucose (mg/dl)	Mean ± St.deviation	119.28 ± 32.98	115.09 ± 20.31
	Range	76-220	80-170
CSF glucose (mg/dl)	Mean ± St. deviation	42.39 ± 9.89	50.54 ± 8.46
	Range	26-70	40-78
CSF glucose/serum glucose	Mean ± St.deviation	0.36 ± 0.05	0.44 ± 0.06
	Range	0.26-0.55	0.36-0.61
WBC count of CSF/µl	Mean ± St.deviation	551.46 ± 228.82	45.68 ± 16.99
	Range	250-1200	10-90
CSF protein (mg/dl)	Mean ± St. deviation	126.03 ± 29.43	57.95 ± 16.09
	Range	80-212	36-110
Serum CRP (mg/L)	Mean ± St. deviation	91.29 ± 46.1	19.72 ± 14.47
	Range	34-190	5-70

The Sensitivity, specificity, positive predictive value and negative predictive value of CSF-CRP and other variables for diagnosis for bacterial meningitis are shown in Table 4 .

Table 4

Variable	Accepted criteria for diagnosis of meningitis	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CSF Glucose	< 40 mg/dl	61%	86%	79%	53%
CSF Glucose/serum glucose	< 0.4	92%	82%	86%	82%
CSF Protein	>100 mg/dl	85%	82%	85%	82%
Neutophil count of CSF	>60 %	78%	86%	88%	76%
Gram smear	Positive	39%	100%	100%	56%
Culture	Positive	21%	100%	100%	50%
Serum CRP	>40 mg/dl	82%	84%	87%	78%
CSF CRP	Positive	75%	91%	92%	75%

CSF –ADA level 10 IU/L as a cut-off value test exhibited 96.66% sensitivity,100% specificity and 100% positive predictive value in differentiating tuberculous from non-tuberculous meningitis.

DISCUSSION

In this study, 108 cases were undertaken as per selection criteria. All the patients were subjected to detailed history taking, clinical examination and necessary investigations including imaging studies and laboratory tests. Diagnosed cases of bacterial and tuberculous meningitis were studied in details and diagnostic ability of CRP and ADA was evaluated in pyogenic, tubercular and viral meningitis.

Consent was obtained from each patient (or their relative in case of altered sensorium) after full explanation of the nature and protocol of the study. Collected data were analyzed using suitable statistical methods as mentioned.

The mean WBC count in pyogenic meningitis group was 551.46 ± 228.82 cells/µl. In contrast to 45.68 ± 16.99 cells/µl in the non-bacterial group. This correlation was statistically significant. (p< 0.0001).Vaidya A K et al, 1987[5] also showed similar result. Mean WBC count difference in two groups was significant. (603.23 ± 250.78 vs. 52.33 ± 18.27). Mean Neutrophil count in pyogenic meningitis group was 56.42 ± 25.88 %.In non-bacterial meningitis group it was 25.55 ± 11.19 %.The two-tailed P value is 0.0002, considered extremely significant.

CSF lymphocyte counts were raised in all the tubercular cases. There was a definitive correlation between the CSF ADA values and lymphocyte count. This is simple to explain as the adenosine enzyme is required for T-lymphocyte proliferation and differentiation. The findings of the present study was consistent with Prasad et al[6] and Gambhir et al[7] studies.

Mean CSF ADA level was significantly higher in TBM patients (**15.056**) as compared to pyogenic meningitis (**6.687**), viral meningitis (**4.671**). In Gambhir et al[7] study, mean CSF ADA level in TBM patients was 9.61±4.10 U/L and was significantly elevated as compared to viral encephalitis and enteric encephalopathy cases. In Prasad et al[6] study, the mean CSF ADA levels were 6.43±1.93; 1.89±0.91; 0.90±0.45 and 0.64±0.57 U/l in tuberculous meningitis, pyogenic meningitis, aseptic meningitis and controls respectively. Mishra OP et al[8] found that mean CSF-ADA level was significantly raised in TBM as compared to partially treated bacterial meningitis patients. The CSF ADA values in pyogenic meningitis cases are intermediate to the respective values of Gambhir et al[7] and Prasad et al[6]. In the aseptic meningitis group, the values of ADA are higher as compared with the respective values in Prasad et al[6], but not in the range of tuberculous meningitis group, as well as ADA levels in control groups of the present study were higher when compared to the values of Prasad et al[6].

The ADA values in tuberculous meningitis group in the present study when compared with the ADA levels in other groups such as pyogenic meningitis, viral meningitis, the p-value was <0.001 and was statistically significant.

In our study CSF CRP was positive in 75% of bacterial meningitis group and in 9% of non-bacterial meningitis group.This correlation was statistically significant. (P=0.0007).Sensitivity, specificity, positive predictive value and negative predictive value of the test were

75%, 91%, 92% and 75% respectively.Similar results were reported by Singh U K et al, 1994 [9],Corrall *et al,* 1981[10] .

A correlation analysis between CSF CRP & CSF WBC count reveals significant positive correlation in presence of bacterial meningitis. ($p<0.001$).This correlation was also positive in aseptic meningitis group but it was not statistically significant.($p=0.85$).Tankhiwale SS et al 2001[11] also found similar result.

Though CSF Neutrophil count in both bacterial & non-bacterial meningitis group had a positive correlationship with CSF CRP it was significant only in bacterial meningitis group.($p = 0.03$).Sormunen P et al 1999[12] reported similar result.

CSF CRP was positive in 75% cases of bacterial meningitis with a specificity of 91% and positive predictive value of 92%.

CONCLUSION

Bacterial meningitis is a potentially devastating illness that requires prompt recognition and early appropriate therapy.This study was done to evaluate the diagnostic utility of CSF-ADA and CRP activity in tuberculous and bacterial meningitis. The mean CSF ADA value in tuberculous meningitis was statistically significant ($p<0.001$) when compared to the CSF ADA values in pyogenic meningitis and viral meningitis.The mean CRP level in bacterial meningitis was statistically significant ($p=0.0007$)when compared to tubercular and aseptic meningitis.

In conclusion, ADA estimation in CSF is not only simple, cost-effective ,rapid and reliable but also a useful differential diagnostic marker of TBM, especially when there is a confusion of differentiating the tuberculous etiology from non-tuberculous. As CSF ADA estimation in TBM can be easily made available and performed with minimal training ,this may find a place as a routine investigation , similarly routine use of CSF-CRP may be useful and patients with positive CRP in the CSF should be treated presumptively for bacterial meningitis. Thus, easily performed rapid CRP determinations can considerably improve the quality of care in meningitis patients, especially in those situations where facilities for performing bacterial cultures of antibiotic susceptibility testing are not available.

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