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To study significance of CSF C- reactive protein and ADA in meningitis

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Abstract
Background – to study significance of Csf C-Reactive Protein And Ada In Meningitis we done this study.
Material and methods – total of 100 patients of meningitis admitted in department of medicine we included with specific inclusion and exclusion criteria and with ethical approval.
Results –CSF CRP was significantly associated with pyogenic meningitis and raised with higher cell count, higher protein levels and lower CSF to blood glucose level, while CSF ADA was significantly raised in tubercular meningitis and higher CSF ADA levels were present in patients with higher cell count, and higher protein levels but no correlation was present between the ratio of CSF and blood glucose.
Conclusion –CRP could be used as a marker of Pyogenic Meningitis and ADA for Tubercular meningitis.

Keywords: Meningitis, Tubercular Meningitis, Pyogenic Meningitis, C - reactive protein, Adenosine Deaminase.

Introduction

Acute infections of central nervous system are among the major syndromes which are the cause of morbidity and mortality, we have to diagnose these conditions early, and with the help of best decisions and treatment life of these patients could be saved[1]. These syndrome include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema. meningitis could be –1bacterial, 2-tubercular,3viral,4-fungal,5-spirochete 6-parasitic. The etiological diagnosis of meningitis remains a problem in clinical practice as csf biochemical analysis & cellular response often overlap. Thus there is a need of rapid & etiological diagnosis of meningitis for better clinical outcome. tests like pcr & elisa are although helpful but are costly, not easily available, and not easily performed. In such circumstances the determination of csf crp and csf ada appears to provide a new dimension to specific diagnosis of meningitis. C-reactive protein is an acute phase reactant of "pentraxin" group of family, discovered in 1930 by tillet *et al*[2]. It is synthesized exclusively in liver and is secreted in large quantities within 6 hrs of an acute inflammatory stimulus in serum or fluids associated with the affected tissues. It is a very sensitive marker of inflammation and identifies those patients whose inflammatory system responds most actively to the stimuli. Raised CSF CRP level in meningitis is due to passive diffusion across the highly inflamed meninges. hence increased serum CRP levels signify acute phase response, thus increased CSF CRP signifies meningeal involvement. CSF CRP testing appears to be an attractive option for rapid diagnosis of pyogenic meningitis and hence many studies have been done to evaluate this role of csf crp[3].Acid-fast staining of csf sediment is the most rapid method for detection of mycobacteria, but this method lacks sensitivity. The diagnostic reference standard, isolation of mycobacterium tuberculosis from csf samples, is insufficiently timed (it requires 1-4 weeks) to aid clinical judgement with respect to treatment, and this method is insensitive if large amount of csf are not used.[4] The use of polymerase chain reaction (PCR) to detect mycobacterium tuberculosis specific DNA may be of potential value. However, the facilities to perform the test are not available in all laboratories and many tests are not affordable because of its high cost. Adenosine deaminase (ADA) is an enzyme of purine catabolism, catalyzing hydrolytic deamination of adenosine to inosine. detection of high level of ada has shown promising results in the diagnosis of

Tuberculous pleural, peritoneal and pericardial effusion.[5] Thus the present study has been designed to evaluate the diagnostic utility of CSF CRP and CSF ADA levels in clinically diagnosed cases of meningitis. An attempt will further be made to correlate these findings with the conventional biochemical & cytological parameters.

Aims and Objectives -1-To study CRP and ADA level in CSF in patient of meningitis.2-To compare CRP and ADA level in CSF in pyogenic meningitis/TBM and viral meningitis.3-To correlate the clinical significance and prognosis with CRP and ADA level in different type of meningitis. 4-To assess the correlation of CSF CRP and CSF ADA with conventional diagnostic parameters of meningitis (CSF cell count, proteins and glucose).5-To calculate diagnostic sensitivity and specificity of CSF CRP in pyogenic meningitis and CSF ADA in TBM.

Material and Methods-A total of 100 patients of suspected meningitis admitted in Department of Medicine and neurology, G.R. Medical College, Gwalior (M.P.) during Nov. 2012 to Nov. 2013 were taken for study. **Inclusion criteria-** Age > 18 yrs and clinical features of Pyogenic meningitis and, 2- CSF Analysis 1-Pleocytosis > 10 to10,000 cells/mm3, neutrophils predominate,2-Protein > 45 mg/dl, 3-Sugar < 40 mg/dl. Inclusion criteria for TBM- Clinical features being the insidious onset of symptoms of meningitis, signs of meningeal irritation and presence of focal neurological deficits. The CSF analysis showing pleocytosis of 10-500 cells/mm^3 predominantly lymphocytes, protein >45mg/dl, sugar<40mg/dl or <40% of blood glucose concentration. Neuroimaging showing evidence of meningeal enhancement, basal exudates or tuberculoma were supportive. For Viral meningitis -Viral meningitis based on clinical and CSF laboratory findings of lymphocytic pleocytosis of 25-500 cells/mm3, protein 20-80 mg/dl, and normal sugar.**Exclusion criteria 1**-Age < 18 yrs**, 2**-Patients with acute infections at sites other than the central nervous system**,**3-Patient in whom lumbar puncture was contraindicated 4-Patient with severe hepatic dysfunction 5-Fungal meningitis.6-Contraceptive use 7-Severe dyslipidemia 8-Steroid

Results – Out of the 100 cases, 16 cases belonged of age group less than 20 years, 45 patients belonged to age group of 21-40 years; 23 belonged to age group of >60 years. Most number of patients belonged to the age group of 21-40 years. In TBM 23 patients (46.93%), in Pyogenic Meningitis 14 patients (46.66) and in Viral Meningitis (38.09%) belonged to the age group of 21-40years.(table 1) In the present study 59 cases were males and 41 cases were females, making up 59 % and 41 % of the cases respectively. Thus there was a male preponderance in our study with a male to female ratio of more than 1.43:1. In the pyogenic meningitis group 13 cases (43.33%) were females and 17 (56.66%) were males, in tubercular meningitis group 18 cases (36.73%) were female and 31 (63.26%) were males, in viral meningitis group 10 case(47.61%) was female and 11 cases (52.30%) were males.**(table no. 2)** In our study fever (96%) was the most common complaint while headache (83%) was the second most common complaint.Other complaint were vomiting (52%) Altered sensorium (45%) Seizure (16%), Focal neurological Deficits (9%), Drowsiness (8%), Stupor (5%), Comatose (4%)**(table no. 3)**The cases of pyogenic meningitis were distributed using different ranges of CSF cell counts & it was found that out of 30 cases,7 cases had cell count <300/mm3; with mean CRP of 12.58 ± 2.230mg/dl, 12 cases had cell count 300-600/mm3, with mean CRP of 16.29 ±3.84 mg/dl. 11 patients had cell count >600/mm3 with mean CRP of 26.15 ±3.99 mg/dl.(table 4) In this study, pyogenic meningitis cases were distributed using different ranges of CSF protein level. out of 30 cases, 11 cases had CSF protein <100mg/dl with mean CSF CRP of 14.2 ± 3.76 mg/dl. 13 cases had CSF protein 100-200 mg/dl with mean CSF CRP of 19.71 ± 6.22 mg/dl. 6 cases had CSF protein >200mg/dl with mean CSF CRP of 26.46 ± 4.19 mg/dl.As we move to the groups with higher CSF protein level, more & more cases had CSF CRP in higher range.(table 5)To study the relation of CSF CRP level with CSF glucose level, cases of pyogenic meningitis were divided on the Basis of the ratio of CSF & blood glucose level & then frequency table was made. about 70% of cases having ratio <0.4. Also observed was that those group with lower ratio are having higher CSF CRP levels. The mean CSF CRP levels was calculated & it was evident that when ratio of CSF to blood glucose increases, the mean levels of CSF CRP decreased. The study population was divided into 3 group with CSF to blood glucose ratio being <0.4, 0.2-0.4 and <0.2, and the difference between mean CRP of this group was found to be statistically significant ($p < 0.001$). **(table no. 6)** Study shows that As the pyogenic meningitis had average level of CSF CRP of 19.04±6.66mg/dl which is much higher as compared to non pyogenic meningitis (viral meningitis 1.71±0.05mg/dl and TBM 1.97±1.24mg/dl). The calculated p value shows that the difference is statistically significant (p value <0.001). Difference between Average level of CSF CRP of viral meningitis and TBM group are not found to be statistically significant (p value 0.342).(table 7) In present study When the CSF CRP cutoff level was taken as >8mg/dl, 28 out of 30 patients of pyogenic meningitis had CSF CRP level > 8mg/dl which was statistically signficant.while it was not true for viral and tubercular meningitis.(table 8)In our study the sensitivity of CRP in diagnosing pyogenic meningitis was 93.33%,specificity of 100%,and 100% of positive predictive value while 97.22% was negative predictive value.(table 9)**.** 15 patients of pyogenic meningitis with altered sensorium had mean CSF CRP level 18.466±7.535. 2 patients with focal neurological deficit had mean CSF CRP level 18.8±8.768. These two groups when compared with mean CSF CRP level of pyogenic meningitis (19.04±6.66) was found to be statistically insignificant (p value 0.8045 and p value 0.9745). 2 patients died in pyogenic meningitis with mean CSF CRP of 16.6±5.65mg/dl which when compared with mean CSF CRP level (19.04±6.66) was found to be statistically insignificant (p value 0.6573).Hence there is no correlation between mean CSF CRP level had clinical presentation and mortality in pyogenic meningitis(table 10). The TBM patients were divided on the basis of CSF cell count level. In group of 0-100 cells/mm^3, 10 patients had mean CSF ADA of 9.75±2.19IU/L. 28 patients with CSF cell count 100-200 cells/mm^3 had mean CSF ADA level of 12.115±2.75IU/L. In group of >200cells/mm^3 11 patients had mean CSF ADA 16.99±4.9IU/L. The difference between three groups was found to be statistically significant (p value <0.0001). Hence with increase in CSF cell count there was increase in CSF ADA in TBM.(table 11)TBM patients were divided on the basis of different CSF protein level. In group

with CSF protein 0-100mg/dl, there are 23 patients with mean CSF ADA 11.05±1.98 IU/L. There are 21 patients with mean CSF ADA of 13.50±4.31 IU/L in group of CSF protein 101-200mg/dl. In group with CSF protein >200 mg/dl, there are 5 patients with mean CSF of 16.04±6.28IU/L. The difference between three groups was found to be statistically significant (p value <0.0001).(table 12) TBM Patients were divided on the basis of CSF glucose/blood glucose ratio. In group of patients with ratio >0.4, 17 patients had mean CSF ADA 13.46±4.63IU/L. In group of patients with ratio between 0.2-0.4, 30 patients had mean CSF ADA 12.12±3.478IU/L. In group of patients with ratio <0.2, 2 patients had mean CSF ADA 11.6±3.95IU/L. The difference between the three groups was found to be statistically insignificant (p value 5.04).Hence there is no correlation between CSF glucose/blood glucose ratio to CSF ADA in TBM.(table 13) Study shows that The TBM group has average CSF ADA of 12.54±3.91 IU/L which is much higher compared to non TBM group (pyogenic meningitis 2.93±0.707 IU/L and viral meningitis 2.62±1.071 IU/L). The difference was statistically significant. However the difference between pyogenic and viral meningitis was statistically insignificant.(table 14)**.** When CSF ADA cutoff level was taken as >10IU/L, 37 out of 49 patients of TBM meningitis had CSF ADA level >10IU/L which was statistically significant(table 15). The diagnostic sensitivity of CSF ADA when in study was 75.51%,while specificity was 100%. Positive predictive value was 100. While negative predictive value was 80.95%(table 16). 25 patients of TBM with altered sensorium had mean CSF ADA level 13.28±5.046 IU/L. 7 patients with focal neurological deficit had mean CSF ADA level 12.77±3.427IU/L. These two groups when compared with mean CSF ADA level of TBM (12.54±3.91) was found to be statistically insignificant (p value 0.541 and p value 0.8906 respectively). 5 patients died in TBM with mean CSF ADA of 12.02±2.97751 IU/L which when compared with mean CSF ADA level (12.54±3.91) was found to be statistically insignificant (p value 0.7169). Hence there is no correlation between mean CSF ADA level had clinical presentation and mortality in TBM. (table 17) In our study, 5 (10.2%) out of 49 patients of TBM expired. 2(6.66%) out of 30 patients of pyogenic meningitis expired. No patients of viral meningitis expired (table 18).

Table No. 1 Age Distribution of patients of meningitis

Age group (years)	Total number of cases	TBM	Pyogenic meningitis	Viral meningitis
< 20	16	9	2	5
21-40	45	23	14	8
41-60	23	9	7	7
> 60	16	8	7	1
Total	**100**	**49**	**30**	**21**

Table No. 2 -Gender Distribution of patients of Meningitis

Gender	Total number of cases	TBM	Pyogenic meningitis	Viral meningitis
Male	59 (59%)	31 (63.26%)	17 (56.66%)	11 (53.38)
Female	41 (41%)	18 (36.73%)	13 (43.33)	10 (47.61)
Total	**100**	**49**	**30**	**21**

Table No. 3-Clinical presentation of meningitis

Clinical presentation	Number	%
Fever	96	96
Headache	83	83
Vomiting	52	52
Seizures	16	16
Focal neurological deficits	09	09
Altered sensorium	45	45
Drowsiness	08	08
Stupor	05	05
Comatose	04	04

Table No. 4-Relation between CSF cell count with CSF CRP in pyogenic meningitis

CSF cell count (cells/mm^3)	No. of Cases	CSF CRP (mg/dl)	
		Mean	SD
<300	7	12.58	±2.230
301-600	12	16.29	±3.84
>600	11	26.15	±3.99

Table No. 5-Relation between CSF protein to CSF CRP in Pyogenic Meningitis

CSF Protein (mg/dl)	No. of Cases	CSF CRP (mg/dl)	
		Mean	SD
<100	11	14.2	±3.766
101-200	13	19.707	±6.22
>200	6	26.46	±4.19

Table No. 6-Relation between CSF Glucose/blood glucose with CSF CRP in pyogenic meningitis

CSF Glucose/Blood Glucose	No. of Cases	CSF CRP (mg/dl)	
		Mean	SD
>0.4	9	14.71	±7.006
0.2-0.4	13	17.93	±4.33
<0.2	8	25.7	±4.33

Table No. 7-Average Level of CSF CRP in the different types of meningitis

	Type of meningitis	Total no.of cases	CSF CRP (mg/dl)
A.	TBM	49	1.97±1.24
B.	Pyogenic meningitis	30	19.04±6.66
C.	Viral meningitis	21	1.71±0.05

A V/s. B - P value <0.001 (statistically significant), B V/s. C - P value <0.001 (statistically significant),C V/s. A - P value 0.342 (statistically insignificant)

Table No. 8-P value of CSF CRP

Type of meningitis	Total no. cases	CSF CRP (>8 mg/dl)	
		No. (%)	p value
TBM	49	0	
Pyogenic meningitis	30	28	<0.0001
Viral meningitis	21	0	

Table No. 9-Diagnostic significance of CRP in relation to pyogenice meningitis

Types of meningitis	Total no. cases	Sensitivity	Specificity	PPV	NPV	Accuracy
Pyogenic meningitis	30	93.33%	100%	100%	97.22%	98%

Table No. 10-Relation between clinical presentation and mortality with CSF CRP in pyogenic meningitis

	No. of Cases	CSF CRP (mg/dl)	
		Mean	SD
Altered sensorium	15	18.466	±7.535
Focal Neurological Deficit	2	18.8	±8.768
Death	2	16.6	±5.65

Table No. 11-Relation between CSF cell count with CSF ADA in TBM

CSF cell count (cells/mm^3)	No. of Cases	CSF ADA (IU/L)	
		Mean	SD
0-100	10	9.75	±2.19
101-200	28	12.115	±2.75
>200	11	16.99	±4.9.

Table No. 12-Relation between CSF protein to CSF ADA in TBM

CSF Protein (mg/dl)	No. of Cases	CSF ADA (IU/L)	
		Mean	SD
0-100	23	11.05	±1.98
101-200	21	13.50	±4.31
>200	5	16.04	±6.28

Table No. 13-Relation between CSF Glucose/blood glucose with CSF ADA in TBM

CSF Glucose/Blood Glucose	No. of Cases	CSF ADA (IU/L)	
		Mean	SD
>0.4	17	13.46	±4.63
0.2-0.4	30	12.12	±3.478
<0.2	2	11.6	±3.95

Table No. 14 -Average level of CSF ADA in the different types of meningitis

	Types of meningitis	Total no. cases	CSF ADA (IU/L)
A.	TBM	49	12.54±3.91
B.	Pyogenic meningitis	30	2.93±0.707
C.	Viral meningitis	21	2.62±1.071

A V/s. B - P value <0.001 (statistically significant), B V/s. C - P value 0.2542 (statistically insignificant), C V/s A. - P value <0.001 (statistically significant)

Table No. 15-P value of CSF ADA

Types of meningitis	Total no. cases	CSF ADA (> 10 IU/L)	
		No. (%)	p value
TBM	49	37	<0.0001
Pyogenic meningitis	30	0	
Viral meningitis	21	0	

Table No. 16-Diagnostic sinificance of ADA in relation to TBM

Types of meningitis	Total no.of cases	Sensitivity	Specificity	PPV	NPV	Accuracy
TBM	49	75.51%	100%	100%	80.95%	88%

Table No. 17-Relation between clinical presentation and mortality with CSF ADA in TBM

	No. of Cases	CSF ADA(IU/L)	
		Mean	SD
Altered sensorium	25	13.28	±5.046
Focal Neurological Deficit	7	12.77	±3.427
Death	5	12.02	±2.97751

Table No. 18-Outcome based on the type of meningitis

Types of meningitis	Outcome	
	Expired	Recovered
TBM	5(10.2%)	44(89.79%)
Pyogenic meningitis	2(6.66%)	28(93.33%)
Viral meningitis	0(0%)	21(100%)

Discussion

The present study was carried out to detect CSF CRP levels & ADA levels in different types of meningitis.Out of the total 100 cases taken for study, 49 cases were of TB Meningitis, 30 cases were of Pyogenic meningitis & 21 cases were of viral Meningitis. The present study was conducted in the Deptt. of Medicine, G.R.M.C. Gwalior, during the period of Nov. 2012 to Nov. 2013. The diagnosis of Meningitis was based of existing history & clinical examination supported by Lab Investigations & findings of CSF examinations.In our study the most of patients belongs to age group of 20-40 years. Same findings were present in previous studies done by Fraser DW *et al.* (1974)[6], Giesler P J *et al.* (1980)[7] & Garner JS *et al.* (1988)[08]. in this present study there was a male preponderance in all the types of meningitis. So was in previous studies done by Bohr V & Hansen B *et al.* (1983)[09] and Schlech WF *et al.* (1985).[10] In our study fever (96%) was the most common complaint while headache (83%) was the second most common complaint. Other complaint were vomiting (52%) Altered sensorium (45%) Seizure (16%), Focal neurological Deficits (9%), Drowsiness (8%), Stupor (5%), Comatose (4%).Similar patterns of presenting complaints were found in the studies of Carpenter *et al.* [11] and Kaplan *et al.* [12]. in this study, it is evident that patients with higher cell count have higher mean CRP levels.This difference was found to be statistically very significant(p value <0.0001).Hence there was significant correlation b/w CSF CRP levels & CSF total count in pyogenic meningitis.This finding is consistent with the previous studies [13,14,15]. In this study we found that patients of pyogenic meningitis with higher protein levels in Csf have higher CRP levels.This finding was statistically very significant (p < 0.0001). this finding is concordant with previous studies[13,14,15].In our study we correlates the ratio of CSF to Blood Glucose ratio with CSF CRP and a inverted relation was found and this finding was statistically significant. In the previous studies[15,16,17] similar correlation was found.In this study mean CRP level of pyogenic menigitis, TB meningitis & viral meningitis were 19.04±.66 mg/dl; 1.97±1.24 mg/dl and 1.71±0.05 mg/dl respectively. This difference between mean level of CSF CRP between pyogenic and non pyogenic (TB and viral) meningitis was found to be statistically very significant (p<0.001). The senstivity & specificity of CSF CRP in pyogenic meningitis was 93.33% & 100% when the cut off was taken as >8gm/dl.

Previous studies also concludes that CRP negativity could be taken as no for pyogenic meningitis[18], and higher levels of crp were presents with gram negative organism incomparison to gram negative organisms[15]. In the present study, we attempt to assess the correlation of CSF CRP with clinical presentation & mortality in pyogenic meningitis. But CSF CRP level did not bear any correlation with clinical presentation & outcomes in pyogenic meningitis in our study and this was true in previous studies also.[6,9,19,20,21]The cases of TBM were distributed using different ranges of CSF cell counts correlation with csf ADA level. & it was found that with increaes in CSF total counts there is increase in CSF ADA in TBM and this is statistically significant.this findings was consistent with past studies.[22,23] In our study,TBM cases were distributed using different ranges of CSF proteins and correlation with CSF ADA was studied, and the findings are suggestive that patients with high protein levels also have higher CSF ADA levels and this findings are statistically significant as per previous studies[22,23.]To study the relation of CSF ADA level with CSF glucose level. And no correlation was found between CSF ADA and blood glucose. this finding was consistent with previous study.[23]In this study, the mean CSF ADA levels of TB meningitis, pyogenic meningitis & viral meningitis were 12.57±3.91 IU/l, 2.93±0.707 IU/l and 2.62±1.071. The difference between mean CSF ADA level between TBM & pyogenic and viral meningitis was found to be statistically very significant ($p<0.0001$). The sensitivity & specificity of CSF ADA in TBM was 75.51% and 100% when the cuff off level was taken as >10 IU/l. this finding is consistent with previous studies [22-27.]in our study, CSF ADA level did not bear any correlation with clinical presentation & outcome in TBM patients.

Conclusion

CSF CRP level was found to be higher in patients of pyogenic meningits when compared to TBM and viral meningitis. CSF ADA level was higher in TBM when compared to pyogenic and viral meningitis.CSF CRP level correlated with CSF cell count, CSF protein & CSF to blood glucose ratio, but there was no correlation between CSF CRP level with clinical presentation and morality in pyogenic meningitis. CSF ADA correlated with CSF cell count & CSF protein level but did not correlate with CSF to blood glucose ratio in TB meningitis. CSF ADA level do not correlate with clinical presentation & mortality in TB meningitis. Using cut off of <8mg/dl for CSF CRP, the sensitivity and specificity of CSF CRP for diagnosis of pyogenic meningitis was found to be 93.33% and 100% respectively. Using cut off level of <10mg IU/l for CSF ADA, the sensitivity and specificity of CSF ADA for diagnosis of TBM was found to be 75.51% and 100% respectively.

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