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Estimation of C-Reactive Protein in Serum and Cerebrospinal Fluid for The Diagnosis of Various Meningitis

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Abstract
Introduction: *Meningitis is a neurological emergency with high mortality and morbidity in the past few years. It is highly desirable to have tools which could be used to diagnose and differentiate between bacterial and non bacterial meningitis with high accuracy. In the best of our knowledge, diagnostic uses of CSF & serum CRP estimation in differentiating bacterial and non bacterial meningitis have been evaluated in very few studies in our country and hence the present study was conducted.*
Aims: *Our aim was to estimate the levels of CRP in CSF and serum in patients of meningitis to differentiate various types of meningitis.*
Material & Method: *The present case control study was conducted in dept of medicine J.L.N. Medical College & Hospital, Ajmer. We include 60 patients each in both study and control group. These patients were further divided into three groups as Pyogenic meningitis (PM) group, Tubercular meningitis (TBM) group and viral meningitis (VM) group.*
Result: *CSF CRP qualitative test was positive in 83.33% cases of PM group while this was negative in all other groups. Serum CRP qualitative test was 100% positive in PM and TBM groups. This was negative in all cases of VM and control groups. In PM group CSF CRP level was 24± 14.98 mg/L (range<6-96 mg/L). In TBM, VM and control groups levels were <6mg/L. In PM group serum CRP level was 128± 110.23 mg/L (range 24-384 mg/L). In TBM group level was 25.85±10.36 mg/L (range 12-48mg/L). In VM and control groups levels were <6mg/L in all cases. Serum CRP value was highly significant in PM and TBM groups in comparison of VM and Control groups. There was no difference between PM and TBM group. CSF CRP level was highly significant in PM group in comparison of TBM, VM and Control groups. There was no difference in TBM groups when compared with VM and Control groups.*
Conclusion: *CSF CRP estimation was highly sensitive to diagnose and differentiate pyogenic meningitis from tubercular and viral meningitis, while serum CRP was highly sensitive to diagnose and differentiate pyogenic and tubercular meningitis from viral meningitis.*

INTRODUCTION

Meningitis is a neurological emergency with high mortality and morbidity in the past few years. Significant advances have been made in the meningitis.

Various pathogens are involved in the etiology of meningitis. The most commonly responsible organisms for pyogenic meningitis are s. pnemoniae in 50% , N. meningitides in 25% , Grp B. streptococci in 10%, L. Monocytogenes in 10% (Roos et al.). Tubercular meningitis is the most common cause of chronic meningitis and incidence in patients with tuberculosis varies from 7 to 12 % (venkataraman et al.). Enteroviruses (polio, coxsackie, Echo) are most common cause of viral meningitis in more than 75% cases.

However CSF protein, sugar and leukocyte count performed routinely to diagnose meningitis but these are not absolutely reliable markers for differentiating various types of meningitis because these are overlapping in their values. In the best of laboratories in India, CSF culture was positive only in 25-40% cases in which CSF gram stains were positive only in 25-30% cases of meningitis (Suvarna Devi Patel et al. Vincent J et al.).

It is highly desirable to have tools which could be used to diagnose and differentiate between bacterial and non bacterial meningitis with high accuracy.

Almost any inflammatory disease will cause detectable quantities of CRP to be present in serum or fluids closely associated with affected tissue (Pepys MB et al). Increased CRP production is an early and sensitive response to most forms of microbial infections and the value of its measurement in the diagnosis and management of various infective conditions has been established (Debeer F.C. et al).

Diagnostic use of CSF and serum CRP estimation in differentiating bacterial and nonbacterial meningitis have been evaluated by few workers (Clarke D et al).

Some workers found that CRP estimation by latex agglutination slide test in CSF had 66-100 % sensitivity to differentiate in pyogenic and viral meningitis. CRP estimation in serum had 95-100% sensitivity in separating pyogenic from viral meningitis(Corral C J et al, Benjamin D R et al, Abramson J S et al , Mcfarlane, Soetiono S et al, Sormunen P et al, Singh U K et al, Singh N et al).

In the best of our knowledge there have been very few studies in this subject in our country and hence the present study was conducted.

AIMS

Our aim was to estimate the levels of CRP in CSF and serum in patients of meningitis to differentiate various types of meningitis.

MATERIAL AND METHODS

The present case control study was conducted in Department of Medicine J.L.N. Medical College & Hospital, Ajmer. Subjects selected for study were >15 years of age. We include 60 patients each in both study and control group.

Inclusion Criteria

1. Clinically suspected cases of meningitis of any etiology and proven by CSF examination were included.
2. Untreated patients or patients admitted in hospital within 24 hrs were being studied

Exclusion criteria: following patients were excluded from study in which CRP is likely to be raised

1. Acute infectious and inflammatory disorders e.g. Acute rheumatic fever , pneumonia, tonsillitis , sinusitis, gout, pancreatitis, Inflammatory bowel disease etc. 2. Tissue destruction e.g. Myocardial infarction 3. Malignancies 4. Collagen diseases e.g. Rheumatoid arthritis, SLE, Sjogren syndrome etc 5.Pregnancy 6.Women on OCPs and IUDs 7. Cerebro-vascular stroke 8. Extensive trauma.

These patients were further divided into three groups as Pyogenic meningitis (PM) group, Tubercular meningitis(TBM) group and viral meningitis(VM)group

PM Group: Only those cases were included in this group which had satisfied 1 or more of the following criteria

1. Positive gram staining of CSF
2. Positive CSF pyogenic culture or blood culture
3. CSF polymorphonuclear pleocytosis with sugar < 50% of Blood sugar levels and protein >50mg/Dl(Bhatt B V et al)

TBM group: Criteria of diagnosis of these cases were biochemical analysis of CSF and raised CSF leukocyte counts with lymphocytic predominance, CSF AFB staining and AFB culture corroborated by history, clinical examination, positive Monteux test, suggestive x-ray and ct findings and others like CSF ADA.

VM Group: Diagnosis based on CSF leukocyte counts 25-500 cells/Cumm with lymphocytic predominance, normal CSF sugar, normal or marginally raised CSF protein ,negative CSF gram and AFB staining ,and CSF and blood culture (Singh U K et al)

Serum and CSF CRP determination:

Serum and CSF CRP determination was done by latex agglutination slide test as per instructions of manufacturer.

Principle

Test was based on principle of agglutination of anti CRP antibody coated polystyrene latex particles by bacterial antigen. If CRP concentration is 6mg/l or greater a visible agglutination is observed . If concentration is <6mg /L then no visible agglutination will be seen (Singh N. et al, Severin WPJ et al).

Procedure

1. Qualitative Test: Sample and reagent were brought on room temperature. 1 drop of undiluted serum/CSF was placed in a well of glass slide by disposable pipette, then 1 drop of latex reagent was added in the specimen and mixed them by mixing stick uniformly. The slide was manually agitated and test was read after 2 minutes.
2. Semi Quantitative Test: Test was done to improve diagnostic specificity and prevent false positive results. A drop of isotonic saline was placed in each well of slide, 1 drop of specimen serum/CSF was added in first well and mixed uniformly. This mixed sample is called 2 times dilution. Took a drop of this solution and added in a drop of saline in second well and mixed them and this mixed sample called as 4 times dilution. This serial dilution was done upto 64 times dilution. A drop of last well was kept safe. A drop of latex reagent mixed in first well and slide is manually agitated. Test was read after two minutes. If agglutination appeared test was called positive in 1:2 dilution. Similar procedure was repeated till agglutination disappeared.

INTERPRETATION OF TEST

Qualitative test: in positive test agglutination occur; in negative test agglutination does not occur.

Semi quantitative method: agglutination in highest dilution corresponds to the amount of CRP present in specimen.

OBSERVATION

Table 1 shows that in study group, 24 out of 60 (40%) cases belonged to pyogenic meningitis, 26 out of 60 (43.33%) cases to tubercular meningitis and 10 out of 60 (16.7%) cases to viral meningitis.

TABLE 1

Cases	Control group (n= 60)	Study group		
		Pyogenic meningitis (PM)	Tubercular meningitis (TBM)	Viral meningitis (VM)
Male	39	12	16	8
Female	21	12	10	2
No of cases	60	24	26	10

Maximum no of case belong to age group of 16-45 years in study group (83.33%) while 31-60 years of control group (65%). Mean age was 31± 15.95 years in study group and 48±13.47 years in control group. There was male preponderance with male female ratio of 1.5:1 in study group and 1.85:1 In control group.

CSF turbidity was present in only PM group (91.67%). All cases of TBM and VM groups showed clear CSF. Cob web formation was present only in TBM group in 53.84% cases.

In most of the cases of PM group (75%) CSF protein levels were >100 mg % and in maximum number of cases (58.33%) levels were 101-500 mg %. In maximum number of cases of TBM group (76.92%) levels were 101-500 mg %. In VM group, 80% cases showed protein levels <40mg%. CSF protein levels were significantly higher ($p<0.001$) in both PM and TBM group in comparison of VM group. CSF protein levels were not significantly higher ($p>0.05$) in PM group in comparison of TBM group.

In most of the cases of PM group (75%) CSF sugar level was <40 mg % and CSF: Blood sugar ratio <0.5. In TBM group maximum number of cases showed sugar level 20 to <40 mg % (69.23%) and CSF: Blood sugar ratio was<0.5 (76.92%). In VM all cases showed sugar level >40mg% and CSF: Blood sugar ratio > 0.5. CSF sugar levels and CSF: Blood sugar ratio were highly significant ($p<0.001$) in PM and TBM group in comparison to VM group. There was no significant difference in CSF sugar levels and CSF Blood sugar ratio ($p>0.05$) between PM group in comparison to TBM group.

CSF leukocyte counts were 101 – 1000 cells/cumm in most of the cases of PM group (83.43%) and in maximum number of cases (58.34%) counts were 101-500 cells/cumm. In most of cases of TBM group 84.62% counts were 101-500 cells/cumm. While in all cases of VM group counts were <100 cells /cumm. CSF leucocyte counts were significantly raised ($p<0.05$) in PM group in comparison to TBM group. These counts were significantly raised ($p<0.001$) in PM group in comparison to VM group while significantly raised in ($p<0.01$) TBM group from VM group.

Polymorphonuclear (PMN) dominance were observed in 75% cases of PM group only. Lymphocytic predominance was present in all cases of TBM and VM Groups. PMN predominance was highly significant ($p<0.001$) in PM group in comparison to TBM and VM group. Lymphocytic predominance was significant ($p<0.05$) in both TBM and VM group in comparison to PM group. However, it was not significant ($p>0.05$) to differentiate TBM and VM.

CSF gram stain and pyogenic culture both were positive in 41.67% cases of PM group while CSF AFB stain and culture was negative in all cases of TBM group. In VM group neither CSF gram stain and nor AFB stain and culture was positive. Overall sensitivity of CSF stain and culture was very low.

TABLE 2 : Showing Serum and CSF CRP (Qualitative) Positivity in Control and Study Groups

Specimen	Control (n=60)		Study group (n=60)					
			PM (n=24)		TBM (n=26)		VM (n=10)	
	No	%	NO	%	NO	%	NO	%
Serum CRP	0	0	24	100	26	100	0	0
CSF CRP	0	0	20	83.33	0	0	0	0

Table 2 shows that CSF CRP qualitative test was positive in 83.33% cases of PM group, while this was negative in all other groups. Serum CRP qualitative test was 100% positive in PM and TBM groups. This was negative in all cases of VM and control groups.

TABLE 3: CSF CRP (Semi quantative) Test Results in Control and Study Groups

Titre (value in mg/L)	Control Group (n=60)		Study Group (n=60)					
			PM (n=24)		TBM (n=26)		VM (n=10)	
	No.	%	No.	%	No.	%	No.	%
1:1 (negative) (<6 mg/L)	60	100	4	16.67	26	100	10	100
1:1 (positive) (6mg/L)	0	0	0	0	0	0	0	0
1:2 (12mg/L)	0	0	8	33.33	0	0	0	0
1:4 (24mg/L)	0	0	8	33.33	0	0	0	0
1:8 (48 mg/L)	0	0	2	8.33	0	0	0	0
1:16 (96mg/L)	0	0	2	8.33	0	0	0	0

Table 3 shows that in maximum number of case of PM (66.66%) CSF CRP levels were 12-24 mg/L. The maximum CSF CRP levels rewarded in 2 patients of PM group was 96mg%. In PM group CSF CRP level was 24± 14.98 mg/L (range<6-96 mg/L). In TBM, VM and control groups levels were <6mg/L.

TABLE 4: Showing Serum CRP (Semi quantitative) Test Results in Control and Study Groups

Titre (value in mg/l)	Control Grp (n=60)		Study Grp (n=60)					
			PM (n=24)		TBM (n=26)		VM (n=10)	
	NO	%	NO	%	NO	%	NO	%
1:1 (negative) (<6 mg/l)	60	100	0	0	0	0	10	100
1:1 (positive) (6mg/l)	0	0	0	0	0	0	0	0
1:2 (12mg/l)	0	0	0	0	4	15.38	0	0
1:4 (24 mg/l)	0	0	4	16.67	18	69.23	0	0
1:8 (48 mg/l)	0	0	6	25	4	15.38	0	0
1:16 (96mg/l)	0	0	8	33.33	0	0	0	0
1:32 (192mg/l)	0	0	2	8.33	0	0	0	0
1:64 (384mg/l)	0	0	4	16.67	0	0	0	0

Table 4 shows that in maximum number of cases of PM group (58.33%), Serum CRP levels were 48-96 mg/l while in TBM group (84.61%) levels were 24-48 mg/l. The maximum CRP levels in PM and TBM groups were 384mg/l and 48mg/l respectively. In PM group, serum CRP level was 128± 110.23 mg/L (range 24-384 mg/L). In TBM group level was 25.85±10.36 mg/L (range 12-48mg/L). In VM and control groups levels were <6mg/L in all cases.

TABLE 5: Showing Sensitivity of Serum and CSF CRP in Study and Control Groups

SPECIMEN	Control (n=60)		Study Group (n=60)						P value		
			PM		TBM		VM		PM	TBM	VM
	No	%	No	%	No	%	No	%			
Serum CRP	0	0	24	100	26	100	0	0	<0.001	<0.001	>0.05
CSF CRP	0	0	20	83.33	0	0	0	0	<0.001	>0.05	>0.05

TABLE 5 shows Serum CRP value was highly significant in PM and TBM groups in comparison of VM and Control groups. There was no difference between PM and TBM group CSF CRP level was highly significant in PM group in comparison of TBM, VM and Control groups. There was no difference in TBM groups when compared with VM and Control groups.

DISCUSSION

The present study revealed that CSF CRP qualitative test was positive only in PM group with sensitivity of 83.33%. Similar observations were found in PM group by Singh N et al who reported CSF CRP test had sensitivity of 84% in PM group. Similar sensitivity in PM group was found in study by Deivanayagam N et al (84%), Kishore R et al (85.7%) Diculencu D et al (73%), Mishra O.P. et al (75%),. Eiden and Yalken (82%) .These results were similar to our study.CSF CRP test was 100% positive in PM group in the study by Ahmed P et al, Pemde H.K. et al, Bengersosh E. et al , Corran C. J.et al, Vaidya A.K. et al, Singh H. et al, Singh UK et al and Macfarlane D.E. et al. However Finley F.O. et al, Przyjalkowski W. et al, Kaldor J. et al, Benjamin D.R. et al found less sensitivity of CSF CRP test in PM group as 58%,62.5%,62.26% and 66% respectively.

Present study revealed that CSF CRP qualitative test had 0% sensitivity in TBM group. Similar observations were reported in TBM group by John M. et al, Donald P.R. et al. However Pemde H.K. et al and Kishore R et al observed sensitivity of 5% and 11.23%, respectively in TBM group.

Present study revealed that CSF CRP qualitative test had 0% sensitivity in VM group. Similar observations reported by Donald P.R. et al, Stearman M. et al, Abrahmson J.S. et al, Vaidya A.K. et al . However, Benjamin D.R. et al and Gray D.M. et al showed 12.5% and 6.06% sensitivity of test in VM group, respectively.

Present study showed that CSF CRP was significantly raised ($p<0.001$) in PM group in comparison to TBM group. Ahmed p. et al and Donald P. et al made similar observations. However Vaidya A.K. et al showed that levels were not significant ($p>0.05$) in PM group in comparison to TBM group.

Present study showed that CSF CRP was significantly raised ($p<0.001$) in PM group in comparison to VM group. Similar observation was reported by Singh U.K. et al, Vaidya A.K. et al and Ahmed P. et al and Gray B.M. et al.

Present study showed CSF CRP was not significant ($p>0.05$) in TBM group in comparison to VM group. Similar observations were reported by Ahmed et al. However, Vaidya A.K. and Donald P.R. et al showed that levels were highly significant ($p<0.001$) in TBM group in comparison to VM group.

The reason for higher CRP value in serum and CSF in Pyogenic meningitis maybe due to greater inflammatory response induced by pyogenic infection than by tubercular and viral infections. The greater CRP response maybe due to extracellular life cycle of bacteria compared with predominant intracellular life cycle of virus.

In present study serum CRP Qualitative Test was positive in both PM and TBM group with 100% sensitivity. Similar observations were found in both PM and TBM groups by Sutinen J. et al, Przyjalkowski W. et al, Petola H. et al and Debeer F.C. et al.

In present study serum CRP qualitative test showed 0% sensitivity in VM group. Similar results were observed by Paltola H. and Valmari P. et al. However, Sormunnen P. et al showed 7% sensitivity of test in VM group.

Present study showed that Serum CRP level were not significantly raised ($p>0.05$) in PM group in comparison to TBM group. Ahmed P. et al and Debeer F.C. et al reported similar observations.

Present study showed that serum CRP levels were significantly raised ($p<0.001$) in PM group in comparison to VM group. Ahmed P. et al, Peltola H. et al, Benjamin D.R. et al and Debeer F.C. et al showed similar observations.

In present study CSF CRP semi quantitative test showed that in PM group CSF CRP mean levels were 24±14.98mg/L. Ahmad P et al , Donald P.R. et al showed that in PM group mean CSF CRP levels were 18.81±8.36 mg/L and 0 to 13.5mg/L respectively.

In present study levels of CSF CRP were <6 mg/L in TBM and VM group. Ahmed P. et al and Donald P.R. et al showed similar observations.

In present study serum CRP semi quantitative test showed that in PM group mean serum CRP levels

were 128±110.23 mg/L (range =24 to 384 mg/L). Similar observations were reported in PM group by Ahmed P. et al, Sormunnen P. et al and Sutinen J. et al. They showed mean serum CRP levels were mean of 119.49±34.72 mg/L, 115±63 mg/L and 207±111 mg/L respectively. Petola H. et al and Debeer F.C. eta l observed the serum CRP levels in PM group were in the range of 80-400 mg/L and 41-400 mg/L respectively.

In present study Serum CRP levels were 25.85±10.36 mg/L (range 12-48mg/L) in TBM group. Similar observations were reported by Ahmed P. et al and Debeer F.C. et al. They showed serum CRP levels were mean of 23.5±6.6 mg/L and 26.3±19.6 mg/L.

The present study showed serum CRP levels were <6mg/L in VM group. Similar observations were reported in VM group by Ahmed P. et al, Clarke D. et al and Debeer F.C. et al.

CONCLUSION

Present study show that CSF CRP estimation was highly sensitive to diagnose and differentiate pyogenic meningitis from tubercular and viral meningitis, while serum CRP was highly sensitive to diagnose and differentiate pyogenic and tubercular meningitis from viral meningitis.

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