

Value of C-Reactive Protein and Adenosine Deaminase Activity in Cerebrospinal Fluid as Rapid Screening Tests In The Diagnosis Of Meningitis

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Abstract: The objective of the study is to assess the utility of C-reactive protein (CRP) levels and adenosine deaminase (ADA) activity in the cerebrospinal fluid (CSF) as rapid screening tests to differentiate various types of meningitis in adults.

Method: CSF samples were obtained from 50 patients of meningitis. Diagnosis of meningitis was based on the clinical presentation and CSF analysis. CRP and ADA activity were assessed in pyogenic, tuberculous and viral meningitis.

Results: Out of total 50 patients who were enrolled in the study, 30 were diagnosed as TBM, 15 as viral and 5 as pyogenic meningitis. The mean ADA activity was 14.6 IU/L in the TBM group. P value of ADA was significant in TBM when a cut off value of 10 was taken. The mean CRP value in pyogenic meningitis was 27.8mg/L. P value of CRP in pyogenic meningitis was significant when a cut off value of 10 was taken.

Conclusions: 2 rapid screening tests- CRP and ADA activity in the CSF can help in the differential diagnosis of pyogenic from non-pyogenic meningitis and tubercular from nontubercular meningitis respectively. CRP being elevated in pyogenic meningitis and ADA activity noted to be higher in TBM. The levels of ADA and CRP were found to be low in viral meningitis.

Key words: Adenosine Deaminase, Cerebrospinal fluid, C-reactive protein, Meningitis.

I. Introduction

Infections involving the central nervous system (CNS) particularly meningitis & Encephalitis are likely to arouse tremendous anxiety in the physicians and patients because, early recognition, efficient decision making and rapid institution of therapy can be life saving.

Reliable, cost effective, rapid screening tests which can be performed in any standard pathology laboratory could be of help in the differentiation of various types of meningitis in Adults.

In this regard, C-Reactive protein (CRP) and Adenosine Deaminase Activity (ADA) can be used as rapid tests in the differential diagnosis of meningitis.

ADA activity is useful in the diagnosis of Tuberculous (TB) meningitis while CRP estimation has been documented to be helpful in diagnosing pyogenic meningitis. The levels of both ADA & CRP are low in viral meningitis.

There have been various studies on the use of ADA in Tuberculous meningitis and CRP in pyogenic meningitis. However, there are no enough number of studies which utilized both ADA & CRP levels and compared their values in various types of meningitis.

Mishra et al.¹ compared CSF ADA activity & CRP activity in TBM and partially treated bacterial meningitis in children. Based on this, sensitivity and specificity of ADA and CRP were 62.5%, 86.9% and 75%, 100% respectively.

ADA estimation in CSF is not only simple, inexpensive and rapid but also fairly specific method for making a diagnosis of tuberculous aetiology in TBM, especially when there is a dilemma of differentiating the tuberculous aetiology from non-tuberculous ones.²

It takes half an hour for the CRP result to be available and maximum of 4 hours for result of ADA activity. Hence, ADA activity and CRP levels in cerebrospinal fluid (CSF) can be used as rapid screening tests in differential diagnosis of meningitis.

This study is done with the objective of using ADA and CRP levels in CSF as rapid screening tests to differentiate various types of meningitis.

II. Materials And Methods

A prospective observational hospital based study was conducted on 50 patients of meningitis who presented to the emergency department and out-patient department of medicine, Sri Venkateswara Medical College, Tirupati during the period between July 2012 and July 2013.

2.1. Inclusion criteria:

1. Age > 18 years , both male and female patients.
2. Patients with clinical features suggestive of meningitis
3. Patients who were willing to give informed written consent

2.2. Exclusion criteria:

1. Patients with acute infections at sites other than CNS.
2. Patients in whom lumbar puncture was contraindicated.
3. Patients with severe hepatic dysfunction.
4. Patients with fungal meningitis.
5. Patients who were not willing to give consent.

2.3 Methodology:

Clinical history, physical findings, investigation reports, treatment modalities, clinical progress and outcome were all recorded on the prepared proforma and CSF samples were obtained from 50 patients who attended emergency department and outpatient department of medicine at Sri Venkateswara medical college, Tirupathi, who fulfilled the inclusion criteria during the period between July 2012 and July 2013. Clinical features taken in to consideration were fever, headache, nuchal rigidity, vomiting, altered mental status, seizures and signs of meningeal irritation.

2.4 Investigations:

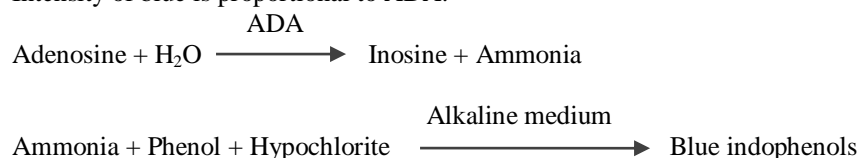
1. Ophthalmic fundii examination
2. CSF analysis –a) Total count b) Differential count c) Proteins d) Sugar e) Gram's staining f) AFB staining g) KOH staining h) Indian ink preparation i) ADA levels j) CRP levels k) Culture
3. CT Brain plain 4. CT Brain contrast if required 5. Chest x ray PA view 6. Blood culture 7. Sputum for AFB staining. 8. TC, DC, ESR, RBS, retro viral antibodies.

METHOD OF ESTIMATION OF CSF CRP: LATEX AGGLUTINATION METHOD:

Principle- CRP causes agglutination of the latex particles coated with anti-human CRP. The agglutination of the latex particles is proportional to the CRP concentration and was measured by turbidometry.

METHOD OF ESTIMATION OF CSF ADA: GUISTI AND GALANTI METHOD

Principle- ADA hydrolyses adenosine to ammonia and inosine. Ammonia further reacts with phenol and hypochlorite in an alkaline medium to form blue iodophenol complex with sodium nitropruside as a catalyst. Intensity of blue is proportional to ADA.



III. Results

Value of CRP in CSF was low in viral meningitis (mean-0.953mg/L) and Tuberculous meningitis (mean-1.367mg/L). In pyogenic meningitis CRP lowest value was 9mg/L and highest value was 48mg/L and the mean value was 27.8 mg/L. With a cut off value of 10, P value of CRP was significant (<0.001) in pyogenic meningitis and thus differentiate pyogenic from nonpyogenic meningitis.

All the patients with pyogenic meningitis have ADA value less than 10 IU/L and the mean value of ADA was 4.2 IU/L. 43.29% of the patients with TBM have ADA of <10 IU/L and 33.33% has 10-20 IU/L. The mean ADA value in TBM was 14.6 IU/L. 86.58% of patients with viral meningitis have ADA < 10 IU/L. The mean ADA value in viral meningitis was 7.66 IU/L.

Table 1: CRP distribution in various types of meningitis:

CRP mg/L	Pyogenic Meningitis	Tuberculous meningitis	Viral meningitis
<1	0	1	3
1 - 10	2	29	12
11-20	0	0	0
21-30	0	0	0
31-40	2	0	0
>40	1	0	0

Table 2: P value of CRP

MENINGITIS	CRP <10	CRP >10	TOTAL	P VALUE
Pyogenic meningitis	2	3	5	<0.001(SIGNIFICANT)
Tuberculous meningitis	30	0	30	0.447(NS)
Viral meningitis	15	0	15	0.603(NS)

Figure 1

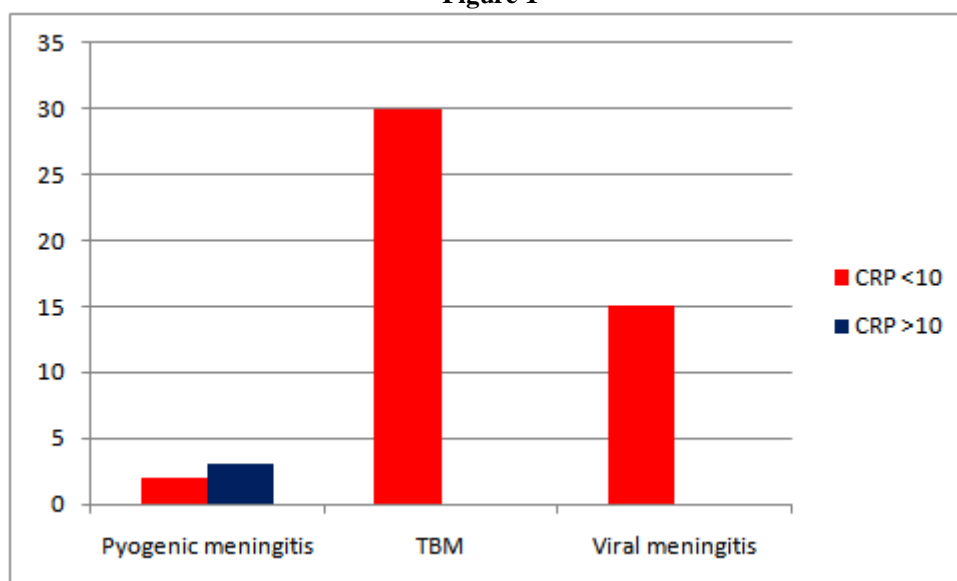


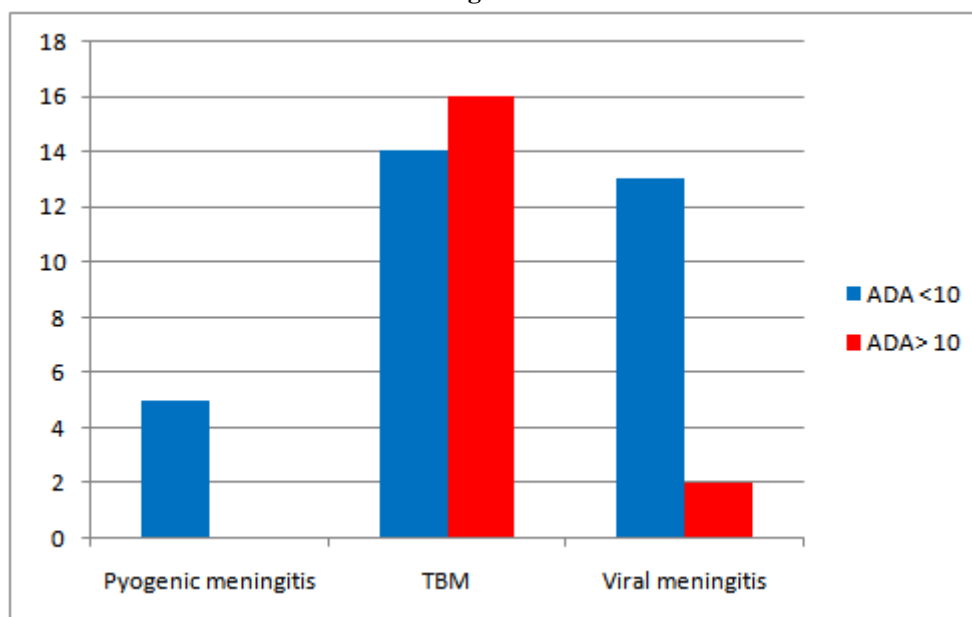
Table 3: ADA in various types of meningitis

ADA IU/L	PYOGENIC MENINGITIS	TBM	VM
<10	5	13	13
10-20	0	10	0
21-30	0	4	1
31-40	0	1	1
41-50	0	2	0

Table 4: p value of ADA

MENINGITIS	ADA <10	ADA > 10	TOTAL	P VALUE
Pyogenic meningitis	5	0	5	0.202(NS)
TBM	14	16	30	0.005(SIGNIFICANT)
Viral meningitis	13	2	15	0.062(NS)

Figure 2:



IV. Discussion

CRP, named for its capacity to precipitate the somatic C-polysaccharide of streptococcus pneumonia. It is one of the first acute phase proteins to be described.³ . Infection with Gram negative bacteria enhances permeability of CRP through the blood brain barrier. Endotoxin Lipopolysaccharide, present in Gram negative bacteria affects the permeability of BBB. Nitric oxide may be involved in this mechanism because, its concentration in CSF is higher in Gram negative meningitis. This possibility is supported by higher potency of Gram negative bacteria to promote macrophage Nitric oxide production.⁴ Recent studies emphasize the fact that absence/ low levels of CRP in serum and CSF especially after 12 hours after manifestation of clinical symptoms strongly rule out bacterial meningitis.⁵

Adenosine deaminase is an enzyme of purine salvage pathway that catalyses the hydrolytic deamination of adenosine to inosine and ammonia. ADA in the CSF can be a sensitive and specific target for the diagnosis of TB meningitis.

Present study was conducted on a total of 50 patients who were diagnosed to have meningitis based on clinical features and CSF characteristics. Of the total 50 patients, 5 patients were diagnosed to have pyogenic meningitis with mean CRP value of 27.8 mg/L, 30 patients were diagnosed to have tuberculous meningitis with mean CRP value of 1.367mg/L and 15 patients were diagnosed to have viral meningitis with a mean CRP value of 0.953mg/L.

In the present study, a cutoff value of 10 was taken to differentiate pyogenic from nonpyogenic meningitis. P value of CRP was found to be significant <0.001 in pyogenic meningitis when compared with TBM (P=0.447, NS) and viral meningitis (P=0.603, NS). Hence CSF, CRP can be used to differentiate pyogenic from nonpyogenic meningitis. The values in the present study are in consistency with the studies of Hemavani V et al.⁶ Riberio MH et al.⁷ Anil Kumar T et al.⁸ Amulya C Belagavi and Shalini M⁹

In present study, a total of 30 patients were diagnosed as tubercular meningitis based on the clinical features and CSF analysis. The mean ADA activity was 14.6 IU/L. 4.2 IU/L in the pyogenic meningitis group (5 patients) and 7.66 IU/L in the viral meningitis group (15 patients). The P value of ADA in TBM was 0.005 which was significant and in pyogenic, viral meningitis was insignificant (p>0.001). The values in the present study are in consistency with the studies of Sang-Ho Choi et al.¹⁰ Chotmongkol V et al. Amulya C Belagavi and Shalini M⁹

Thus, CSF CRP and ADA can be used as rapid screening tests to differentiate various types of meningitis in adults at a cut off value of 10. However, the results should be interpreted with caution based on history and clinical features.

V. Conclusion

Of the 50 patients with meningitis, the incidence of TBM (60%) was more common followed by viral (15%) and pyogenic meningitis (5%). With cut off value of 10, CRP 'P' value was significant in pyogenic

meningitis compared to TBM & Viral meningitis. Mean CRP value in pyogenic meningitis was 27.8 mg/L. With a cut off value of 10, ADA 'P' value was significant in TBM compared to viral & Pyogenic meningitis. Mean ADA value in TBM was 14.6 IU/L. The mean ADA & CRP values in viral meningitis were 7.66 IU/L, 0.953 mg/L respectively which were not significant compared to other groups.

The method of estimation of CSF CRP & ADA is simple, inexpensive and the results are available quickly. Thus, CRP & ADA levels in CSF can be used as good screening tests to differentiate pyogenic, tuberculous & viral meningitis. Early Diagnosis & treatment can bring down the mortality & morbidity of patients with meningitis.

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