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A Study of the Diagnostic Role of CSF Adenosine Deaminase (ADA) in Various Types of Meningitis

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Abstract

***Background**: Meningitis is caused by bacteria, viruses, and fungi. The incidence of tubercular meningitis is very high in developing countries like India. The clinical features of meningitis depend on the causative organisms and CSF analysis can help in differentiating the various causes of meningitis. The important goal for the management of meningitis includes early recognition and prompt treatment. Determination of CSF-ADA (Adenosine Deaminase) levels may be one of the easy and reliable methods for differentiating tubercular from nontubercular meningitis.* ***Methods:** This prospective study was conducted in the Department of General Medicine in collaboration with the Departments of Neurology, Biochemistry, and Microbiology of Prathima Institute of Medical Sciences, Nagunur, Karimnagar. The following tests important clinical details for patients suspected of meningitis were done. It included information regarding the duration of fever, signs of meningeal irritation, focal neurological deficits and cranial nerve palsies were elicited. Laboratory examination included CSF analysis (appearance, cell counts, biochemistry, Gram, AFB & India ink stain), blood counts, blood culture & sensitivity, Mantoux test, HIV test.* ***Results:** The percentages of tuberculous, bacterial and viral meningitis were 48%, 26%, and 26% respectively. The CSF ADA level was highest in tuberculous meningitis, the mean value being 24.5 U/L. The mean value of ADA in bacterial meningitis was 4.54 U/L. Using 10U/L as cutoff value of CSF-ADA we found Sensitivity=100%, Specificity = 92.85%, Positive Predictive Value = 91.66% Negative Predictive Value =100%.* ***Conclusion:** CSF ADA is a simple, time saving, a cost-effective indirect test that helps in identifying the type of meningitis, differentiating tuberculous from nontuberculous etiology. Further among the nontuberculous group of meningitis, ADA values are lowest in viral meningitis and thus it can aid in distinguishing bacterial from viral etiology.*

***Keywords**: Meningitis, CSF-Adenosine Deaminase (ADA) levels*

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Introduction

The most common cause of meningitis is infections by bacteria, viruses, fungi, and other microorganisms. The other causes of noninfectious meningitis include chemicals, drugs, inflammatory conditions like CNS Sarcoidosis, SLE and Bechet's syndrome [1]. Meningitis is a medical emergency because it is life-threatening since the meninges are close to the brain and spinal cord. The long term consequences of improper recognition or treatment of meningitis include neurological like deafness, epilepsy, cognitive defects and hydrocephalus [2]. Analysis of CSF is the most commonly used method to diagnose or exclude meningitis. Management of meningitis is done according to the diagnosis; it involves the administration of appropriate antibiotics, antivirals or anti-tubercular agents. Steroids are required to be used in some situations to prevent complications from over whelming inflammation. In developing countries, the frequency of tuberculous meningitis ranges from 7-21% [3]. The usual presentation is with gradual

onset of symptoms and slowly progresses to irreversible neurological complications and death if not diagnosed and treated early. One of the methods of diagnosis is the detection of acid-fast bacilli by light microscopy of the CSF smear it is rapid and specific however the detection rate is up to 30 -40% [4]. Mycobacterial culture on Lowenstein- Jensen (L-J) medium is higher than microscopy it needs a very period of incubation. The other latest tests such as assays based on nucleic acid amplification have been used but they are costly and are some of its limitations especially in developing countries [5]. It has been found that the use of Adenosine Deaminase (ADA) estimation is very useful. ADA is an enzyme in the purine salvage pathway and its presence in abundance in active T-lymphocytes. The T cells released during the cell-mediated immune response to tubercle bacilli can be detected in CSF and it has been used to differentiate tuberculous and non-tuberculous meningitis [6-9]. Studies have found that ADA can be used for differentiating the tuberculous pleural, pericardial effusion and ascites from other causes. Since it is simple, rapid and cost-effective and having acceptable specificity to distinguish TB meningitis from other causes of meningitis we in the present study tried to estimate the CSF ADA levels in patients with suspected meningitis and find its usability for differentiating the different types of meningitis in patients of this study.

Materials and Methods

This prospective study was conducted in the Department of General Medicine in collaboration with the departments of Neurology, Biochemistry, and Microbiology of Prathima Institute of Medical Sciences, Nagunur, Karimnagar. Institutional Ethical committee permission was obtained for the study. Written consent was obtained from the patients of the study. The patients were selected from those presenting with clinical features suggestive of meningitis. The clinical suspicion of meningitis was from symptoms and signs like fever, headache, nausea/vomiting, neck rigidity, presence of Kernig's and/or Brudzinski's sign, altered sensorium, any focal neurological deficit, cranial nerve palsies, seizures and/or signs of cerebral dysfunction ranging from confusion, delirium, declining level of sensorium from lethargy to coma. The inclusion criteria were all the cases suspected of meningitis that were above the age of 15 years. The exclusion criteria were patients less than 15 years of age and patients in whom lumbar puncture was contraindicated like those suffering from coagulopathy, increased INR ratio and platelet counts less than one lakh per cubic millimeter, those suffering from local skin reactions or known spinal cord tumors. History, clinical examination and laboratory investigation were carried out in all patients. Important clinical details regarding duration of fever, signs of meningeal irritation, focal neurological deficits and cranial nerve palsies were elicited. Laboratory examination included CSF analysis (appearance, cell counts, biochemistry, Gram, AFB & India ink stain), blood counts, blood culture & sensitivity, Mantoux test, HIV test. Based on clinical and laboratory data, the patient's type of meningitis was confirmed and treatment started accordingly.

Collection of CSF sample: This was done by lumbar puncture. Color and cobweb formation was noted. Total and differential cell count was estimated. Biochemical analysis of protein, sugar, chloride, and globulin was done. Microbiological workup of the sample was done to find out the etiological organism with the help of Gram's, Ziehl-Nelson and Indian ink stains. About 2 ml of CSF was used to find out the ADA level.

Estimation of CSF ADA: CSF Adenosine deaminase level was measured at 37°C according to the method of Guisti and Galanti based on the Berthelot reaction that is the formation of colored indophenol complex from ammonia liberated from adenosine and quantified spectrophotometrically [5]. One unit of ADA is defined as the amount of enzyme required to release 1 mmol of ammonia/min from adenosine at standard assay conditions. Results were expressed as units per liter per minute (U/L/min). The different types of meningitis were diagnosed on the CSF analysis and cytochemistry. Tuberculous meningitis was positive if CSF yielded M. Tuberculosis or positive Ziehl - Nelson stain. The other diagnostic parameters included the presence of a

lymphocytic pleocytosis in the CSF with high protein content and low glucose content, negative bacterial and fungal cultures. Viral meningitis was diagnosed if there was predominantly lymphocytic pleocytosis in the CSF with a normal or mildly raised protein content, normal glucose content and negative bacterial, fungal and mycobacterial cultures. All the data was recorded in the MS Excel spreadsheet and the analysis was done with SPSS version 17 on windows format.

Results

Tuberculous meningitis occurred more in the age group of 21– 40 years. Bacterial meningitis was seen mainly in patients < 20 years of age. Viral meningitis was seen in all age groups. Out of n=50 cases, 33 were males. Of the 50 cases, n=24 had tuberculous meningitis. Viral and bacterial meningitis constituted n=13 cases each shown in table 1. The percentages of tuberculous, bacterial and viral meningitis were 48%, 26%, and 26% respectively. All three types of meningitis (tuberculous, bacterial and viral meningitis) were more common in males (table 2).

Table 1: Age and the distribution of Meningitis cases

Age in years	No. of cases	Tuberculous Meningitis	Bacterial Meningitis	Viral Meningitis
16- 20	11	2	5	4
21-40	19	12	3	4
41-60	16	9	4	3
>60	4	1	1	2
Total (%)	50 (100%)	24 (48%)	13 (26%)	13 (26%)

Table 2: Sex wise distribution of Meningitis

Sex	No. of cases	Tuberculous Meningitis	Bacterial Meningitis	Viral Meningitis
Male	33	16	9	8
Female	17	8	4	5
Total	50	24	13	13

Table 3: Mean CSF ADA level in various types of Meningitis

Type of Meningitis	No. of cases	Mean CSF ADA Level (U/L)
Bacterial Meningitis	13	4.54 ± 1.12
Tuberculous Meningitis	24	24.5 ± 5.36
Viral Meningitis	13	2.65 ± 0.57

Table 4: Diagnostic Performance of CSF ADA (at 10 U/L cut off) concerning the type of Meningitis

Disease	Test (CSF ADA values)	CSF ADA values	Total
	>10	<10	
TBM	22 (a)	2 (c)	24 (a+c)
Non TBM (BM&VM)	0 (b)	26 (d)	26 (b+d)
Total	22 (a+b)	28 (c+d)	50

P value *= < 0.001 (statistically significant),* ***Sensitivity****=100%,* ***Specificity*** *= 92.85%,* ***Positive Predictive Value*** *= 91.66%,* ***Negative Predictive Value*** *=100%*

The CSF ADA level was highest in tuberculous meningitis, the mean value being 24.5 U/L. The mean value of ADA in bacterial meningitis was 4.54 U/L and viral meningitis patients had the lowest mean ADA value of 2.65U/L (Table 3).

Of the 50 patients, 28 had ADA <10 U/L. Out of this, 26 cases belonged to the viral and bacterial meningitis groups and the rest 2 had tuberculous meningitis. About 22 patients had CSF ADA >10 U/L and all of them belonged to the tuberculous meningitis group (table 4).

Of the TBM patients, majority had CSF protein level more than 80mg/dl. Most of the viral meningitis patients had protein level less than 40 mg/dl. Among the bacterial meningitis patients, protein level was found to be between 40 – 80 mg/dl predominantly (table 5).

Table 5: CSF Protein level according to the type of Meningitis

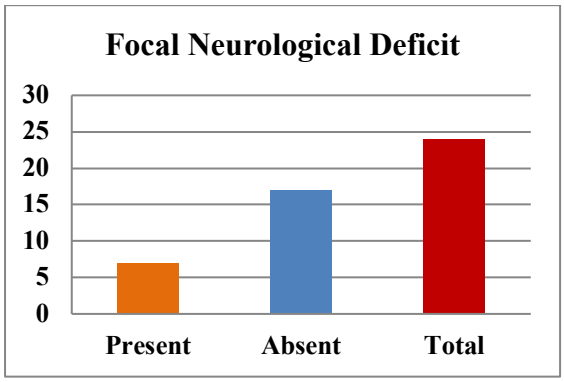
CSF Protein (mg/dL)	No. of cases	TBM	BM	VM
<40	11	0	1	10
40 - 80	24	11	10	3
80 - 120	10	8	2	0
>120	5	5	0	0
Total	50	24	13	13

Table 6: CSF sugar level according to the type of Meningitis

CSF Sugar (mg/dl)	No. of cases	TBM	BM	VM
<40	29	17	12	0
>40	21	7	1	13
Total	50	24	13	13

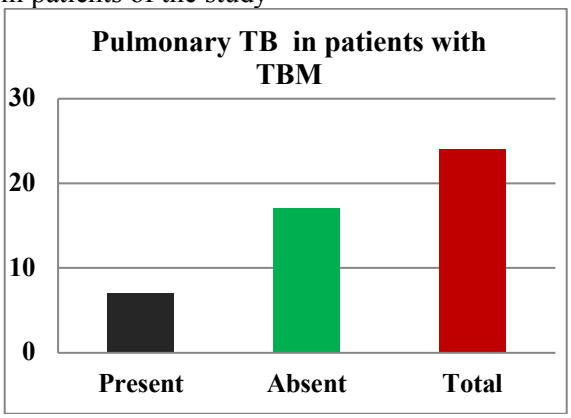
In the TBM group, 14 patients had cell count less than 50 cells/µL and 10 patients had cell count more than 50 cells/µL. Most of the bacterial meningitis patients had a cell count of greater than 100 cells/µL. All the viral meningitis patients had a cell count of lesser than 50 cells/µL. In tuberculous and bacterial meningitis groups, the majority had low sugar (<40 mg/dl). All the viral meningitis patients had normal CSF sugar (table 6). Of the 24 TBM patients, 14 had Mantoux positivity and 10 were Mantoux negative. Of the 14 Mantoux positive TBM patients, 12 had ADA more than the cut off level i.e. more than 10U/L.

Graph 1: Presence of Focal Neurological Deficit in TBM



Of the n=24 TBM patients, 7 had developed focal neurological deficits and cranial nerve palsies. Of these n=7 patients, one had Right hemiparesis, one had left monoparesis, and one had paraparesis. N=2 patients had developed 3rd cranial nerve palsy and another n= 2 had developed 6th cranial nervepalsy (Graph 1)

Graph 2: Presence of Extraneural tuberculosis in patients of the study



Of the n=24 patients with TBM, n=8 had positive findings in neuroimaging in the form of basal exudates (4.17%), meningeal enhancement (20.83%) and both meningeal enhancement and basal exudates together in 8.33% patients (table 7).

Table 7: CT/MRI Findings in patients with TBM

CT/MRI Findings	No. of cases	% of cases
BE	1	4.17
ME	5	20.83
BE & ME	2	8.33
Normal	16	66.67
Total	24	100

Discussion

The urgency in the treatment of meningitis is due to the potential to cause irreversible brain damage. Clinical features, CSF analysis, biochemistry, and microbiological results may take time and in some cases, they may also remain inconclusive. Hence in suspected meningitis patients, specific treatment for tuberculous or non-tuberculous (bacterial or viral) is usually begun based on presumptive clinical diagnosis. In these circumstances, CSF ADA estimation may be useful because it is simple, cost-effective and rapid. In the present study, a total of n=50 patients clinically suspected cases of meningitis admitted in Prathima Institute of Medical Sciences and Hospital were studied. We found in this study that out of n=50 cases n=24(48%) were tubercular meningitis, Bacterial meningitis was diagnosed in n=13(26%) and viral meningitis in n=13(26%) of cases. The CSF-ADA levels in this study were higher in patients with tuberculous meningitis. The findings of this study were consistent with the results of similar studies done in this field [10-15]. We used a cutoff value of 10U/L for diagnosis of tuberculous meningitis and the results then showed 100% sensitivity and 92.85% specificity the PPV was 91.66% and NPV was 100% the p values were <0.001 which was considered highly significant. AK Agarwal et al; [16] in their study established that CSF ADA levels of 10U/L cutoff value showed the sensitivity of 87.5% and specificity of 83.33% in differentiating tuberculous meningitis from non-tuberculous meningitis. BK Gupta et al; [9] in their study established that CSF-ADA levels of 10U/L exhibited 94.73% sensitivity and 90.47% specificity in differentiating tuberculous from non-tuberculous meningitis. Prasad R et al; [17] used a cut off value of CSF-ADA at 3.3 U/L and found the sensitivity of 100% and specificity of 97.87%. R Baheti et al; [18] used a cutoff value of 6.5 U/L, sensitivity was found at 95.83% and specificity was 92.85%. The mean ADA level in CSF in cases with tuberculous meningitis of this study was 24.5 U/L. It is considerably higher than those reported by other workers (11.7- 15.7 U/L). The range of CSF ADA level in TBM in our study was 6.0 U/L to 84.3 U/L. The mean ADA level in CSF in bacterial meningitis and viral meningitis in this study was 4.54 U/L and 2.65 U/L respectively. Focal neurological deficits and cranial nerve palsies were found in n=7 TBM patients. Mantoux positivity in tuberculous meningitis was found in n=14 cases out of n=24 cases. Extraneural TB was found in n=7 TBM patients in the form of pulmonary TB. In TBM patients, positive CT/MRI findings were observed in n=8 of the n=24 patients. In the case of bacterial meningitis, gram stain positivity was found in n=9 of the n=13 cases. It has been reported that cranial nerve palsies occur in 20-30% of cases of tuberculous meningitis. The sixth cranial nerve is commonly affected [19]. The optic nerve involvement with consequently Vision loss may be the dominating feature. Clinical presentation depends largely on the location of lesion patients may be seen with headache, seizures, papilledema and other signs of increased intracranial tension [20].

Conclusion

The present study concluded that most of the cases 48% were of tuberculous meningitis. The levels of CSF-ADA were >10U/L in all the cases of tuberculous meningitis. Hence CSF ADA is a simple, time saving, a cost-effective indirect test that helps in identifying the type of meningitis, differentiating tuberculous from nontuberculous etiology. Further among the nontuberculous group of meningitis, ADA values are lowest in viral meningitis and thus it can aid in distinguishing bacterial from viral etiology.

Conflict of Interest: *None declared*
Source of Support: *Nil*
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