Evaluation of CSF ADA Levels as a Diagnostic test for Tuberculous Meningitis and its Correlation with Adverse Neurological Outcome

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ABSTRACT

Introduction: Early diagnosis and treatment of TBM is of great importance, thereby a more sensitive diagnostic test is needed to establishing the diagnosis. To evaluate CSF-ADA level as a diagnostic test for TBM and its correlation with poor neurological outcomes.

Material and methods: This was a prospective study conducted over one year comprise of 67 patients of TBM in which stage of disease, neurological outcomes, abnormalities on neuroimaging were assessed and CSF parameters were analysed and correlated with CSF ADA levels at the time of admission. Diagnosis of TBM made by using clinicopathological diagnostic criteria of Thwaites for TBM. Stage of disease was assessed by MRC Staging and neurological outcomes during hospitalization were assessed by Modified Rankin Score.

Results: Mean CSF ADA for MRC Stage I was 10.3±11.29 while it was 16.63±8.24 for Stage III which was significant ($p<0.01$). CSF ADA levels significantly correlated with neurological deficit. Mean CSF ADA level was 15.38± 10.92. Using cut off value 10 U/L the sensitivity was 76% and specificity was 85% for diagnosis of TBM. Patients with higher mean CSF ADA values at admission had poor neurological outcomes.

Conclusions: CSF ADA level has significant value in diagnosing TBM. CSF ADA levels correlate with stage of disease at time of presentation, neurological outcomes and can be use as a prognostic indicator.

Keywords: CSF ADA, TBM, Thwaites Criteria, Modified Rankin Score, MRCS Stage

INTRODUCTION

Tuberculous meningitis is a common infectious disease of the central nervous system (CNS) in developing countries. Early diagnosis and treatment with Anti Tubercular drugs and active management of the complications are of great importance to prevent the irreversible neurologic sequel and death. CNS tuberculosis accounts for ~5% of extra pulmonary cases and approximately 1% of all cases of tuberculosis, and carries a high mortality and a distressing level of neurological morbidity.[1] This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed.[2]

A definitive diagnosis of tuberculous meningitis depends on identifying Mycobacterium tuberculosis in the cerebrospinal fluid (CSF) by direct staining or culture.[3] The diagnosis also depends on the clinical manifestations of sub acute or chronic meningitis with lymphocytic CSF and low CSF glucose levels.[2] However, other forms of meningitis may mimic tuberculous meningitis. Adenosine deaminase (ADA) is an enzyme involved in purine catabolism. It is considered as an indicator of cell-mediated immunity and is found mainly in T lymphocytes.[4] Detection of CSF ADA activity in the diagnosis of tuberculous meningitis has been reported with good results.[5-7]

The aim of our study was to evaluate the diagnostic role of CSF ADA in tuberculous meningitis and its correlation with the stage of disease, neuroimaging findings and adverse neurological outcomes (mortality and morbidity).

MATERIAL AND METHODS

This was a non – interventional, hospital based prospective study conducted over a period of one year from July 2011 to August 2012. In this study we included 67 patients of Tubercular meningitis in which stage of disease, neurological outcomes, abnormalities on neuroimaging were assessed and various CSF parameters were analysed and correlated with CSF ADA levels at the time of admission. Patients aged 13 years or more who presented with a clinical picture of meningoencephalitis (Fever, headache, vomiting, neck stiffness, altered sensorium, seizures or focal neurologic deficit) and with CSF abnormalities suggestive of Tuberculous meningitis were included in this study. Patients aged less than 13 years, with haemorrhagic CSF tap, with abnormal CSF finding of non-infective etiology like subarachnoid haemorrhage, peripheral nervous system disease and those with CSF findings suggestive of fungal/ pyogenic/ aseptic meningitis were excluded from the study. A thorough neurological examination was done to diagnose meningitis and its complications. CSF was analysed for Total cell count, differential cell count, total protein, sugar, Gram staining, AFB staining, India ink staining, CSF ADA (adenosine deaminase) levels, *Mycobacterium tuberculosis* culture, fungal culture and CSF tuberculosis-polymerase chain reaction (TBPCR). Neuroimaging (Computed tomographic Scan/ Magnetic Resonance Imaging) was done.

Morbidity and mortality was assessed using the modified Rankin scale (MRS). The modified Rankin Scale[8] is a commonly used scale for measuring the degree of disability. The scale runs from 0-6, running from perfect health without symptoms to death. To label the patients as a case of tuberculous meningitis 'criteria of Thwaites'[9] was used. This criteria is described as *M. tuberculosis* isolated from CSF or

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How to cite this article: Manoj Kumar Mathur, Ajeet Kumar Chaurasia, NC Dwivedi, Sandeep Kumar Singh. Evaluation of CSF ADA levels as a diagnostic test for tuberculous meningitis and its correlation with adverse neurological outcome. International Journal of Contemporary Medical Research 2016;3(4):1064-1067.

Focal neurological deficit	Number of patients	Mean CSF ADA U/L	p value
Hemiparesis	9	22.47±11.03	<0.01
Cranial nerve palsy	7	10.67±6.92	>0.01

Table-1: Correlation of CSF ADA levels with focal neurological deficits

MRC stage	No. of patients	Mean CSF ADA U/L	p value
Stage I	9	10.3±11.29	>0.05
Stage II	44	15.89±10.92	<0.01
Stage III	14	16.63±8.24	<0.01
Total	67		

Table-2: Correlation of CSF ADA levels with MRC staging at admission

Clinical meningitis with negative Gram and India ink stains, plus sterile bacterial and fungal culture, plus one or more of the following: 1- Cranial CT scan consistent with tuberculous meningitis hydrocephalus, oedema, basal meningeal enhancement 2- Chest radiograph consistent with active pulmonary Tuberculosis and 3- Good response to anti-tuberculosis chemotherapy. These patients were classified based on the disease stages as proposed by the Medical Research Council (MRC)[10] -stage I: fully conscious and no focal deficits; stage II: conscious but with inattention, confusion, lethargy, and focal neurological signs such as cranial nerve palsies; stage III: stuporus or comatose, multiple cranial nerve palsies, or Complete hemiparesis.

These patients were treated for tuberculous meningitis as per the standard protocol. The stage of the disease, abnormalities on neuroimaging, morbidity and mortality during hospitalisation were assessed and correlated with CSF-ADA levels at the time of diagnosis.

STATISTICAL ANALYSIS

The following Statistical tools were employed to analyze the results obtained from the study- Mean, Standard Deviation, 't' test for independent samples and correlation coefficient.

RESULTS

A total of 67 patients were included in this study. Among these 42 were male and 25 females. Mean duration of illness at the time of presentation was 42 days. Fever (n-67,100%), headache (n-64, 95.52%) and altered sensorium (n-48, 71.64%) were the commonest symptoms. Neurological deficit present in 9 patients (13.4%) and cranial nerve palsy observed 6 patients (8.9%). At the time of presentation 44 patients (65.67%) were in Medical Research Council Stage II. At the time of discharge 33 patients (49.25%) were in Modified Rankin scale (MRS) Stage 2 (slight disability). 10 patients (14.92%) showed worst outcome-Stage-6 (Died). CSF total cell count ranged from 04 to 800 cells per millilitre cube. 39 patients (58.2%) had CSF glucose values < 40 mg%, mean value was 42.81±35.12. CSF protein concentration ranged from 55.9 to 1600 mg/dl and mean protein concentration was 272.85 ± 226.29mg/dl. CSF ADA level ranged from 4.7 U/L to 75.2 U/L and mean CSF ADA was 15.38± 10.92. 51 patients (76.11%) had CSF ADA level >10 U per litre. Mean CSF ADA in 6 TB PCR positive patients was 13.91±4.58 U/L. 17 patients (25.39%) had hydrocephalus as a major neuroimaging finding in their CT scan.

We correlated CSF ADA levels with different parameters. Mean CSF ADA value 20.17±11.09 was for patients who presented with duration of illness more than 15 days upto 1 month. There was significant correlation of CSF ADA level with neurological deficits in term of hemiparesis ($p<0.01$) when compared with the patients who did not had neurological deficit. While other findings we observed such as Cranial nerve palsies had no such correlation (Table 1). CSF ADA levels correlated with medical research council (MRC) staging at the time of admission. At the time of presentation mean CSF ADA levels found to be highest in MRC Stage III -16.63±8.24 ($p<0.01$) (Table 2). CSF ADA levels also correlated with Modified rankin scale (MRS) at the time of discharge. Patients who were in MRS Stage 4 or 5 had significantly higher mean CSF ADA values than those who were in Stage 1 or 2 ($p<0.01$) (Table 3). We found an increasing trend of mean CSF ADA values with increase in CSF protein concentration with correlation coefficient of 0.90 showing a positive relationship. We also found a decreasing trend of mean CSF ADA values with increase in CSF glucose concentration. CSF ADA levels also correlated with neuroimaging finding (hydrocephalus, basal exudates, infarcts) which was found to be non significant ($p>0.01$) when compared with patients who had normal CT scans (Table 4).

DISCUSSION

In our study 46 patients (68%) presented within one month duration of illness and 28 patients (41.79%) presented within 15 days of illness. Mean duration of presentation was 42 days. CSF ADA levels correlated well with duration of symptoms. Mean value of ADA was 20.17±11.09 for the patients presented with duration of more than 15 days upto 1 month. Ribera et al[5] in there study found that there was a significant rise in levels of ADA during the first 10 days of therapy followed by a gradual decline. We also found similar observsations in our study. Ruth M. Rottbeck et al[11] found that fever was present in 66.7% and altered sensorium in 23.8% of tuberculous meningitis patients. S Hosoglu et al[12] found in there study that headache and fever were the most common symptoms, occurring in 92% and 82.5% of cases respectively. In our study we also found that Fever (n-67,100%), headache (n-64, 95.52%) and altered sensorium (n-48, 71.64%) were the commonest presenting symptoms, which is similar to findings reported by Ruth M. Rottbeck et al and S Hosoglu et al. In our study focal neurological deficits was observed in 9 patients (33%) and Cranial-nerve palsy was noted in 7 patients (19%) before the start of therapy. In our study 44 patients(65.67%) were in MRC Stage II at the time of presentation. In study by S. Hosoglu et al[12] at the time of admission 32.0% patients presented in MRC stage I, 39.5% as stage II and 29.5% as stage III while Khanna et al[13] found that at the time of admission, 85.3% patients were in MRC stage III and 13.5% in stage II. The difference

Modified Rankin Scale	No. Of Patients	Mean CSF ADA U/L	p value
Stage 0(Normal)	0	-	-
Stage 1(No Significant- Disability)	16	9.5±11.01	
Stage 2(Slight Disability)	33	16.02±10.99	
Stage 3(Moderate Disability)	2	10.84±5.96	
Stage 4(Moderately Severe Disability)	4	35.18±12.95	<0.01
Stage 5(Severe Disability)	2	15.92±7.04	<0.01
Stage 6(Death)	10	15.43±8.29	<0.01
Total	67		

Table-3: Correlation of CSF ADA levels with Modified rankin scale at discharge

CT scan/MRI (brain)	Number of patients	Mean CSF ADA U/L	p value
Hydrocephalus	17	13.34±11.64	>0.01
Basal Exudates	4	16.55±8.69	>0.01
Infarct	8	14.86±7.14	>0.01
Normal	33	14.81±10.92	

Table-4: Correlation of CSF ADA with neuroimaging findings

obsereved in various study may be because of time of referral from primary care hospitals. According to Girgis NI et al[14] the initial stage of disease at presentation was a major prognostic indicator for mortality. In their series, the mortality rate was 18% for medical research council stage I TBM, 34% for stage II, and 72% for stage III.

CSF ADA in the study ranged from 4.7 U/L to 75.2 U/L and mean CSF ADA level was 15.38± 10.92. Mean CSF ADA level in 6 patients who were CSF TB-PCR positive was 13.91±4.58 U/L. Using cut off value of CSF ADA > 10 U/L for the diagnosis of tuberculous meningitis the sensitivity was 76% and specificity was 85%. In our study specificity of estimation of CSF ADA levels was similar to study by Kashyap et al[15] but sensitivity was low probably due to small sample size (n-67) in comparison to their study (n-117). CSF total cell count ranged from 04 to 800 cells per millilitre cube and mean cell count was 133.52±181.16. Mean protein concentration in our study was 272.85 ± 226.29. There was strong correlation of CSF ADA levels with CSF protein levels which ranged from 9.67±9.46 to 27.45± 11.09 U/L. Correlation coefficient of 0.64 showing a positive relationship. Mishra et al[16] also reported significant correlation between CSF ADA levels and CSF protein concentration in there study. Malan et al[17] and Satya Vati Rana et al[7] found a positive correlation of ADA levels in CSF with CSF proteins. Mean CSF glucose value was 42.81±35.12 in our study. CSF ADA levels correlated with CSF glucose levels showing an inverse relationship with correlation coefficient of -0.13 which was not significant. Amulya C Belagavi[6] and Chotmongkol et al[18] also observed similar findings.

In our study 17 patients (25.39%) had hydrocephalus as a major neuroimaging finding in their CT scan followed by infarct (n-8, 14.20%) and basal exudates (n-4, 6.34%). We found that there was no significant correlation of CSF ADA levels with neuroimaging finding of hydrocephalus (p>0.01). This finding was opposite to the finding of Khanna et al[13] who observed hydrocephalus in 16.9% patients, exudation in basal cisterns in 10.8% and infarcts in 4.8% patients and found significant correlation of CSF ADA levels with of Hydrocephalus(p<0.01). Bhargava et al[19] found hydrocephalus in 83%, cerebral infarction in 28% of patients which was higher to the finding in our study. CSF ADA levels significantly correlated with neurological deficit in terms of hemiparesis (p<0.01) while other findings such as cranial nerve palsies do not had such correlation. According to Jakka S. et al[20] CSF ADA measurements have been found to be useful in predicting poor neurological outcomes (neurological deficit, morbidity and mortality) in tuberculous meningitis cases. Khanna et al[13] also observed that CSF ADA levels were found to be higher in patients of tuberculous meningitis with remnant neurological deficit and in those who expired. In our study mean CSF ADA value was 10.3±11.29 for MRC Stage I, 16.63±8.24 for Stage III and this difference was significant (p<0.01). Patients with advanced stages of tuberculous meningitis had higher CSF ADA values. Khanna et al[13] also found similar results. The outcomes in terms of morbidity and mortality at the time of discharge after an average 15 days of hospital stay were correlated significantly with CSF ADA levels. Patients with higher mean CSF ADA values at admission had poor outcomes (neurological deficit, death, MRS stage4/5/6). Patients who expired had significantly higher CSF ADA values (p<0.01). Similar observation was found by Khanna et al[13] in their study where CSF-ADA levels were maximum for the worst outcome (death), while for the best outcome (no symptom) they were found to be minimum.

CONCLUSION

CSF ADA level has significant value in diagnosing tuberculous meningitis. A value of >10 CSF ADA level may be regarded as cut of value with good sensitivity and specificity for diagnosing tubercular meningitis. CSF ADA levels correlate with stage of disease at time of presentation, neurological outcomes and can be use as a prognostic indicator.

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

Submitted: 21-02-2016; **Published online**: 18-03-2016