VOLUME-6 | ISSUE-4 | APRIL - 2017 • ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

STUDY OF CSF ADA IN TUBERCULAR MENINGITIS

Pediatrics

KEYWORDS: CSF-cerebro-spinal fluid, ADA-adenosine deaminase, TBM-tubercular meningitis

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ABSTRACT

Aims and objective: To Study correlation of CSF-ADA level in TBM. **Study design:** A prospective study was conducted civil hospital, BJMC Ahmedabad, Department of pediatrics **Results:** In this study among 50 cases of meningitis, 34(68%) patients were of TBM. Most common presenting symptom in TBM patients was fever(94%). Among all TBM 19(55.88%) patients had CSF protein value between 100-200mg. 02(05.88%) patients with value >200 mg% had adverse prognosis. Maximum patients 25(73.53%) had CSF cell count <100 cells/ cu.mm with mononuclear cell predominance. Most common changes on imaging was hydrocephalus (9/20 on CT and 6/14 on MRI). CSF ADA was positive in 21(61.77%) patients. Out of 16 nonTB patients,3 had positive CSF ADA value.CSF ADA has 61.77% sensitivity and 81.25% specificity with positive and negative predictive value of 87.5% and 50%, we thus conclude that CSF ADA is an important investigation in early diagnosis of TBM.

Introduction:

Tuberculosis still ranks as a major health problem in India. As per Tuberculosis Association of India (1975) nearly 1.5% of the population at any given time is suffering from tuberculosis.

Neuro-tuberculosis is one of the serious complications of primary-TB. TBM is the main cause of death and disability in children with tuberculosis. In early 50s the mortality was high with low recovery rate, improvement in treatment leads to improved recovery, with an increase in serious sequel as the diagnosis and treatment are often delayed. Hence the most important aspect is prevention of serious complications of primary infection by the use of anti tubercular drugs under Directly observed Treatment Short Course (DOTS) in Revised National Tuberculosis Control Programme (RNTCP) of the Government of India.

Though the most common form of tuberculosis is pulmonary, most dangerous is that affecting the CNS TB posses major diagnostic challenge due to its varied presentation which requires early diagnosis and treatment.

As the gold standard for diagnosis of TBM is positive smear/culture for AFB in CSF, which has a poor yield and long waiting period. Rapid diagnosis of TBM is important. ADA is an enzyme catalyzing the deamination of adenosine to inosine. The enzyme is widely distributed in human tissues especially high in T lymphocytes, marker of cellular immunity, activity is elevated in those diseases in which there is a cell mediated immune response. Numerous studies have demonstrated that CSF ADA estimation is useful in the diagnosis of TBM and can differentiate it from normal subjects or from patients with other neurological disorder.

The present study is an attempt to examine the cases of TBM respect to the clinical features and CSF ADA as diagnostic measure in TBM with statistical analysis with comparison of CSF ADA levels of TBM with pyogenic-meningitis and other.

Material and methods:

A detailed history and clinical examination done which was recorded in the proforma. The clinical diagnosis of TBM and others made on the basis of history, clinical examination including detailed neurological examination. Samples of CSF were taken for cells, biochemical investigations and CSF-ADA.

Prospective study done from June 2015 to December 2016 at tertiary care center admitted for suspicion of meningitis between 6 month to 12 yrs of age at pediatric ward

Results:

TABLE-1 INCIDENCE OF DIFFERENT TYPES OF MENINGITIS

Types of Meningitis	Number of Patients	Percentage(%) (n=50)
Tuberculous meningitis	34	68
Pyogenic meningitis	09	18
Other	07	14
Total	50	100

In this study total of 50 cases studied, 34(68%) patients were of TBM, 09(18%) of pyogenic meningitis and 07(14%) other.

Most common presenting symptom in TBME patients was fever (94%). Other symptoms were convulsion(32%), vomiting(29%), Headache(32%) and altered-sensorium (26%). Among all patients of TBM 17 had meningeal signs. The Mantoux test was found to be positive in 20 patients (58.82%)

TABLE-2 CSF MICROSCOPIC PICTURE

Disease group	Cells/cu mm	Polymorphonuclear cells	Mononuclear	Protein	Sugar
TBM	20-1400	0-70%	30-100%	37-100	5-74

In this study CSF cell count ranged from 20-1400 per cu mm. with predominance of mononuclear cells 30-100%. Out of 34 cases of TBM 13(38.23%) patients had CSF protein <100 mg%. 19 (55.88%) patients had value between 100-200 mg% and 2(05.88%) patients had value > 200 mg%.

Those having CSF protein value > 200 mg% had adverse prognosis.

In this study 25(73.53%) patients had CSF cell count <100 cells/ cu.mm, 05 (14.70%) had counts between 100-300/cu.mm, 03 (08.82%) had count above 300/cu.mm. There was lymphocytic predominance, smear for AFB by ZN technique from CSF sample was not positive in any patient.

TABLE-3 ANALYSIS OF CT SCAN/ MRI BRAIN FINDING IN TUBERCULOUS MENINGITIS

CT scan was done in 20/34 (58.82%) of cases, MRI brain was done in 14/34(41.18%) cases.

TYPE OF LESION	CT SCAN BRAIN	MRI BRAIN
Basal exudates + Hydrocephalus	04(20%)	01(07.14%)
Hydrocephalus	09(45%)	06(42.85%)
Basal exudates	01(5%)	
Infarct	02(10%)	02(14.28%)
Tuberculomas	04(20%)	05(35.71%)
Total no	20(58.82%)	14(41.18%)

In this study CT-scan finding are 4 patients had CT suggestive of basal exudates and hydrocephalus, 9 hydrocephalus, 1 basal exudates, 2 infarct and 4 had tuberculomas.

MRI finding are,1 patient had basal exudates and hydrocephalus, 6 hydrocephalus, 2 infarct and 5 tuberculomas.

TABLE-4 ANALYSIS OF ADA IN CSF IN DIFFERENT TYPES OF

MENINGITIS

Types	No. of Cases	CSF ADA	
		Positive	Negative
Tubercular	34	21(61.77%)	13(38.23%)
Pyogenic	09	02(22.22%)	07(78.78%)
Other	07	01(14.29%)	06(85.71%)
TOTAL	50	24(48.00%)	26(52.00%)

In this study we measured ADA activity in CSF by ***modified calorimetric of GalantiGuisti*** and cut off level taken as 6.51u/L.

CSF ADA was positive in 21(61.77%) patients of TBM and negative in 13(38.23%). Out of 16 non-TB patients 03 has positive CSF ADA value and 13 patients has negative value. Comparing CSF ADA in TBM and other types, CSF ADA was Positive in 61.77% Patients, applying chi-square test, correlation between CSF ADA positivity and TBM Was highly significant (Chisquare(x2)=8.065(i.e > 3.84 so p<0.05).

Table 5 Correalation of CSF ADA:

Disease	True positive		False negative		Sensitivity
	No	(%)	No	(%)	
TBM	21	61.77	13	38.23	61.77%

In the present study, it is evident that 21/34 patients (61.77%) had ADA values above the cutoff Point (True positive). while 13/40 patients (38.23%) had values below the cutoff point (False negative) suggestive that sensitivity of the test for present study is 61.77%.

Table 6 Correlation of CSF ADA:

Disease	False positive		True negative		Specificity
	No	(%)	No	(%)	
Non TBM	03	18.75	13	81.25	81.25%

While in the 16 other patients not having TBM 13/16 had ADA values below the cut-off level (true negative) and 3 /16 patients had values above the cut off level (false positive) thus specificity 81.25%. CSF ADA level as 6.5IU as cut off value exhibited **61.77% sensitivity and 81.25% specificity**.

Positive and Negative predictive value of CSF ADA is 87.5% and 50% for diagnosis of TB meningitis .

Discussion:

In the study out of a total of 50 cases studied, 34 (68%) patients were of tuberculous meningitis, 09 (18%) patients were of pyogenic meningitis and 07 (14%) were other. Most common presenting symptom in TBME patients was fever (94%) followed by convulsion(32%) and Headache(32%) studies by **Michelle Whiteman et al and Laura J. Christie et al** also suggest that most common presenting symptom of TBME was fever in 54% and 75% of patients respectively. Out of all TBME patients 17(50%) had meningeal signs. The Mantoux test was found to be positive in 20 patients (58.82%) . Various authors have reported negative TT in 5-50% **(TT negative- Udani PM 39.60%, Raj Narain 35.00%)** of cases. The skin test may be negative in severely debilitated or malnourished patients, those on corticosteroids, immune compromised or those with advanced or terminal stage of the disease, and do not rule out TBM patients.

Among all TBM patients maximum no of patients 19 (55.88%) patients had CSF protein value between 100-200 mg , and 02 (05.88%) patients had value > 200 mg% had adverse prognosis .

In this study maximum patients 25(73.53%) patients had CSF cell count <100 cells/cu.mm with mononuclear cell predominance where as **Rashmi Kumar et al** observed a CSF cell count of 137 per cumm with 75% mononuclear cells and **A.M.A Abbasi et al** observed a CSF cell count of 156 per cumm with 82% mononuclear cells.

Smear for AFB by ZN technique from CSF sample was not positive in any patient. Although **Western studies** have quoted the incidence of smear positivity in up to 87% of cases, while in Indian studies; smear positivity is there in only 10-50% of cases. The reason for low positivity may be due to technical expertise or partial immunity, partial treatment before referral.

CT scan brain maximum patients shows changes of hydrocephalus 09(45.00%) while on MRI brain out of 14 patients 06 (42.85%) shows hydrocephalus followed by tuberculoma 05(35.71%), Various studies are also suggest that hydrocephalus is more common in tuberculous MENINGITIS like **R Leiguarda et al (89.23%), S Bhargava et al (83.05%).**

In this study ADA activity in CSF cutoff level was taken as 6.51u/L. CSF ADA was positive in 21(61.77%) patients of TBM and negative in 13(38.23%) . Further among 16 non-TB patients 3 had positive CSF ADA value and 13 patients has negative value. Comparing CSF ADA in TBM and other types, CSF ADA was Positive in 61.77% Patients, applying chi-square test, correlation between CSF ADA positivity and TBM Was highly significant (Chisquare(x2)=8.065(i.e > 3.84 so p<0.05). CSF ADA has 61.77% sensitivity and 81.25% specificity***. Other studies are also suggestive of high sensitivity and specificity of CSF ADA in differentiating TBM from other MENINGITIS like Kashyap et al (sensitivity 82%, specificity 83%), Gautam et al (sensitivity 85%, specificity 88%), Chotmngkol et al (sensitivity 75%, specificity 93%). Positive and negative predictive value of 87.5% and 50%, Bharat kumar Gupta et al showed positive and negative predictive value of CSF ADA is 90% and 95%.***

Conclusion:

We found no correlation between CSF ADA levels and % CSF proteins. From the above study, we thus conclude that CSF ADA is an important investigation in early diagnosis of TBM. Though overlap in values with pyogenic meningitis is seen, when related with cellular count & type, it can differentiate TBM from pyogenic meningitis.

However although our study is a very small study, we advocate that ADA estimation in CSF should be a baseline investigation in any suspected case of meningitis as it clearly differentiates pyogenic meningitis and normal. Thus we can avoid unnecessary, multiple drug therapy.

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