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RESEARCH ARTICLE

VALIDITY OF ADENOSINE DEAMINASE LEVELS IN CEREBROSPINAL FLUID IN TUBERCULOUS MENINGITIS- A STUDY FROM NORTH BIHAR

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ABSTRACT

Background: Incidence of Tubercular meningitis (TBM) in developing countries is 7-12%. About 25 % patients have poor prognosis because of delay in diagnosis. The aim of the present study is to find a simple, rapid, cost effective diagnostic test in differentiating tubercular etiology from other causes.
Methods: Sixty-two patients admitted to our tertiary hospital with symptoms and signs of meningitis were selected and divided into two groups: tubercular (n=39) and pyogenic (n= 23), depending upon the accepted criteria. CSF examination done in each patients and adenosine deaminase (ADA) level estimated. Cut off value of ADA kept at or above 10 IU/L for tubercular meningitis.
Results: The mean age of patients with tubercular meningitis was 39.07 ± 16.67 years and that of pyogenic meningitis 34.35 ± 16.73 years. Out of 39 tuberculous patients, 33 patients were found to be having CSF ADA at or above the cutoff value of 10 IU/L while six had below cutoff value. In tubercular meningitis, the ADA level in CSF ranged between 7 to 112 U/L with mean± SD as 35.72 ± 32.83 IU/L, while in pyogenic meningitis, the ADA level ranged between 2.4 to 7 IU/L with a mean ± SD as 4.21± 1.35 IU/L. On comparison between two groups, the CSF ADA level found to be statistically highly significant ($P < 0.001$).
Conclusions: our study showed that estimation of ADA in CSF is not only simple, inexpensive and rapid but also fairly specific method for making a diagnosis of tuberculous meningitis. For this reason we recommend CSF ADA estimation in TBM.

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INTRODUCTION

Tuberculous meningitis (TBM) is a common cause of morbidity and mortality. The diagnosis depends upon cytochemical analysis of cerebrospinal fluid (CSF). Many a times the differentiating tuberculous meningitis from non-tuberculous meningitis becomes very difficult. Incidence of TBM in developing countries is 7-12%. Delay in diagnosis and so in the start of effective treatment results in poor prognosis and sequalae in up to 25% of cases (Garcia-Monco, 1999). Adenosine deaminase (ADA) is an enzyme in the purine salvage pathway that catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine respectively with the release of ammonia. It plays important role in differentiating lymphoid cells and is present in abundance in active T-lymphocytes whose concentration is inversely proportional to the degree of differentiation (Sharma, 1996). Its levels are ten times higher in T-lymphocytes than in erythrocytes. ADA is released by T cells during cell mediated immune response (CMI) to the tubercle bacilli. ADA is now being recognized as a marker of cell mediated immunity particularly as a marker of T lymphocyte activation. Many researchers uses Adenosine deaminase levels (ADA) to differentiate tubercular disease from non-tubercular (Malan *et al*., 1984; Piras *et al*., 1972; Kashyap *et al*., 2006; Gupta *et al*., 2010; Gupta *et al*., 2010). We tried to estimate ADA levels in CSF in TBM and to find out its role as a sensitive, accurate, rapid, and affordable diagnostic tool that will work in resource-limited settings in confirming the tubercular etiology in cases of meningitis.

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MATERIALS AND METHODS

The study conducted between February 2016 and January 2017 at Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar, a tertiary care centre, in 62 patients with meningitis after

prior consent and ethical approval. The diagnosis of meningitis was made on the basis of clinical symptoms and signs like headache, fever, nausea, vomiting, neck rigidity, presence of Kernig's and/or Brudzinski's sign, altered sensorium, any focal neurological deficit with no other general medical condition explaining them.

SPSS 19.0 was used for statistical analyses. Patient's ages were described as mean ± standard deviation. Continuous variables were compared by the *t*-test and dichotomous variables were compared by Fisher's exact test for two by two comparisons or Pearson χ^2 for greater than two responses.

Patients were divided into two groups:

Group A –Tubercular Meningitis (n=39)

Group B - Pyogenic Meningitis (n =23)

Presence of above signs and symptoms with one or more of the following criteria was adopted to label a case as tuberculous meningitis:

- Bacteriological proof of presence of Mycobacterium tuberculosis.
- Biopsy showing caseating granulomas.
- Clinico- radiological findings consistent with Tuberculosis.
- Definite clinical and radiological improvement in one month after specific anti-tubercular treatment.

therapy. Lumbar puncture was done in each case and at least 2ml of CSF was collected in a sterile vial. Hemorrhagic CSF was excluded from the study. This CSF was subjected to biochemical and microscopic examination. ADA activity was estimated in all these patients by the method of Guisti (Giusti, 1974) and was expressed as U/L. Cutoff reference range of 10 U/L CSF ADA was taken as positive.

Observation

Out of 62 patients with meningitis admitted to our hospital, 50 were male and 12 female (Table 1). Thirty-nine patients (62.9%) with tubercular meningitis and twenty-three (37.1 %) pyogenic meningitis. The mean age of patients with tubercular meningitis was 39.07 ± 16.67 years and that of pyogenic meningitis 34.35 ± 16.73 years. Clinically fever was present in 60 (96.77 %), headache in 49 (79.03 %), and vomiting in 44 (70.96 %) patients. Among tubercular meningitis, 6 (15.38 %) had seizure. Meningeal signs – neck rigidity in 46 (74.2 %), Kernig's sign in 37 (59.68 %) and Brudzinski's sign in 18 (29.03 %) patients. None of the meningeal signs shown to have statistical significance (P < 0.001). Out of 39 tuberculous patients, 33 patients were found to had CSF ADA at or above the cutoff value of 10 IU/L while six had below cutoff value. Of the 23 patients with pyogenic meningitis, one had CSF ADA at or above the cutoff value. In Group A (TBM), the ADA level in CSF ranged between 7 to 112 IU/L with mean± SD as 35.72 ± 32.83 IU/L. While in Group B (pyogenic meningitis), the ADA level ranged between 2.4 to 7 IU/L with a mean ± SD as 4.21± 1.35 IU/L. On comparison between

Table 1. Demography and clinical features of all patients with meningitis

Characteristic		Tubercular meningitis (Group A), N = 39	Pyogenic meningitis (Group B), N =23	All (Group A+B), N= 62	P-value
Sex	Male	36 (92.3 %)	14 (60.9 %)	50 (80.6 %)	0.716
	Female	03 (7.7 %)	09 (39.1 %)	12 (19.4 %)	
Age (Mean ± SD), Years		39.07 ± 16.67	34.35 ± 16.73	37.32 ± 16.67	
Fever	Yes	37 (94.8 %)	23 (100 %)	60 (96.8 %)	0.98
Headache	Yes	29 (74.3 %)	20 (86.9 %)	49 (79.0 %)	0.08
Vomiting	Yes	22 (56.4 %)	22 (95.7 %)	44 (71.0 %)	0.327
Seizure	Yes	06 (15.4 %)	00 (0.0 %)	06 (9.7 %)	0.582
Neck rigidity	Yes	31 (79.5 %)	15 (65.2 %)	46 (74.2 %)	0.058
Kernig's sign	Yes	17 (43.6 %)	20 (86.9 %)	37 (59.7 %)	0.004
Brudzinski's sign	Yes	06 (15.4 %)	12 (52.2 %)	18 (29.0 %)	0.029

Table 2. Distribution of the Cases According to Set Criteria and CSF ADA Levels

GROUP	Number of cases	ADA Level In IU/L	N (%)	MEAN ± SD	P- VALUE
GROUP A (Tubercular meningitis)	39	ADA ≥ 10	33 (84.6 %)	40.67±33.39	
		ADA < 10	6 (15.4 %)	8.47±0.81	
GROUP B (Pyogenic meningitis)	23	ADA ≥ 10	1 (4.3 %)	-	<0.001
		ADA < 10	22 (95.7 %)	4.21±1.35	
TOTAL	62		62	24.03±30.13	

For Pyogenic meningitis presence of above signs and symptoms for a short period of time and typical CSF findings were elevated pressure, neutrophilic pleocytosis, i.e., cell count > 100 WBC/cu. mm consisting of more than 90% polymorphs, elevated protein > 40 mg%, sugar ≤ 50% of the blood sugar, cloudy or turbid appearance, culture and gram staining may be positive for bacteria and full recovery without anti-tuberculosis

two groups, the CSF ADA level found to be highly significant (P < 0.001). In six (9.7 %) patients with tuberculosis meningitis the CSF ADA level was less than 10 IU/L. (Table 2).

DISCUSSION

We prospectively analyzed 62 patients with meningitis. On the basis of clinical features and cerebrospinal fluid examination

findings patients were divided into two groups: Tubercular meningitis (n= 39) and Pyogenic meningitis (n=23). Adenosine deaminase (ADA) level in CSF estimated in all patients and its level in tubercular meningitis patients were compared with those in pyogenic meningitis patients as control. There are various methods like demonstration of AFB in CSF, CSF culture, CSF cell count, CSF sugar, CSF protein and genomic amplification to confirm the etiology of TBM but visualization of AFB in direct smears or in cultures of CSF is usually difficult and in most cases negative (Molavi *et al*., 1985). Sometimes CSF cytology, sugar and protein levels may not be able to differentiate between the two. The genomic amplifications by PCR are not widely available and are costly. CSF - ADA estimation was reported to be useful in diagnosing TBM and to differentiate TBM from pyogenic and aseptic meningitis (Malan *et al*., 1984; Blake, 1982). We found that in TBM group the mean (± SD) CSF ADA was 35.72 (± 32.83 IU/L), while in pyogenic meningitis it was 4.21 (± 1.35 IU/L). A study by Karsen H *et al* in 24 patients with TBM found a mean ADA values of 28.34 ± 14.83 IU/L (Karsen *et al*., 2011). In our study CSF - ADA level 10 IU/L as a cutoff value differentiate tuberculous from non-tuberculous meningitis. There was a highly statistically significant difference in the CSF - ADA levels of meningitis due to tuberculosis and pyogenic etiology ($P < 0.001$) (Table 2). In about 84.6 % (33/39) of tubercular meningitis patients the CSF- ADA level was more than 10 IU/L. Results of our study indicate that ADA levels in CSF are of considerable value in diagnosis of TBM and in differentiating this disease from others because a cut-off CSF - ADA level of 10 IU/L exhibited fairly high statistical significance.

Conclusion

We found that estimation of cerebrospinal fluid ADA with a cut off value of 10 IU/L is highly statistically significant in diagnosing tubercular meningitis. It's cheap, simple, inexpensive, rapid and fairly specific method for making a diagnosis of tuberculous meningitis. For this reason we recommend CSF ADA estimation in tubercular meningitis.

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