

ADENOSINE DEAMINASE ACTIVITY IN CEREBRO-SPINAL FLUID FOR DIAGNOSIS OF TUBERCULOUS MENINGITIS*

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Summary : Adenosine deaminase activity (ADA) was studied in cerebrospinal fluid of 29 cases of tuberculous meningitis, 15 cases of pyogenic meningitis, 12 cases of aseptic meningitis and 20 controls (patients without any neurological disorders who were given spinal anaesthesia). The mean cerebrospinal fluid adenosine deaminase activity was respectively 6.43 ± 1.93 ; 1.89 ± 0.91 ; 0.90 ± 0.45 and 0.64 ± 0.57 IU/L in tuberculous meningitis, pyogenic meningitis, aseptic meningitis and controls. The adenosine deaminase activity in tuberculous meningitis cases was significantly higher. The sensitivity and specificity of this test for diagnosis of tuberculous meningitis was 100% and 97.87% respectively with ADA value of more than 3.30 IU/L. Thus, adenosine deaminase activity in CSF, a relatively inexpensive and easy procedure, can be of great value in the diagnosis of tuberculous meningitis.

Introduction

Tuberculous meningitis still remains an important cause of morbidity and mortality in India. Due to lack of early and timely diagnosis of tuberculous meningitis, the fatality rate remains high. Even when it is not fatal, the sequelae are distressing and disabling. Thus, early and correct treatment is essential for a successful outcome in patients of tuberculous meningitis.

Any test which facilitates a correct and rapid diagnosis of tuberculous meningitis should be very valuable. The definitive diagnosis of tuberculous meningitis depends on the detection

of acid fast bacillus and culture of *Mycobacterium tuberculosis* in cerebrospinal fluid. However, culture is positive with varying degree and the facility is not always available. The characteristic CSF cytological and biochemical changes are also variable and may even be absent.

Adenosine deaminase is an enzyme of purine catabolism leading to hydrolytic deamination of adenosine to inosine and ammonia. Adenosine deaminase has shown promising results in the diagnosis of tuberculous pleuritis, peritoneal and pericardial effusions and tuberculous meningitis.^{1,5} The present study was conducted to confirm the usefulness of adenosine deaminase assay for diagnosis of tuberculous meningitis.

Material and Methods

A total of 56 clinically suspected cases of meningitis admitted in Gandhi Memorial and Associated Hospitals, Lucknow, were studied. The selected patients had no previous history of any specific therapy. Twenty patients without any neurological disorder who had to be given spinal anaesthesia were included as normal controls. The 56 cases comprised tuberculous meningitis: 29, pyogenic meningitis: 15, and aseptic meningitis: 12 cases.

All the cases were examined clinically and thoroughly investigated as follows:

- Haematological-Hb%, TLC and DLC,
- Mantoux test.
- Sputum/Gastric aspirate for AFB.
- Chest X-ray, X-ray skull (if needed).

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* Paper presented at the 45th National Conference on TB and Chest Diseases held at Rohtak in January 1991.

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Cerebrospinal fluid:

- (i) Physical-colour, presence of cobweb.
- (ii) Biochemical-protein, sugar.
- (iii) Microscopic examination-TLC, DLC.
- (iv) Bacteriological studies-smear for AFB, culture for Mycobacterium tuberculosis and pyogenic organisms.
- (v) Cerebrospinal fluid ADA level estimation spectrophotometrically.⁶

Observations

Table 1 gives the ADA values in the various groups. The mean ADA activity was 6.43 ± 1.93 , 1.89 ± 0.91 , 0.90 ± 0.45 and 0.64 ± 0.57 IU/L in tuberculous meningitis, pyogenic meningitis, aseptic meningitis and controls respectively. The higher level of ADA in tuberculous meningitis was statistically significant ($p < 0.001$)

Table 2 shows that the mean ADA level was more (7.43 ± 1.24 IU/L) in the culture positive cases of tuberculous meningitis compared with the culture negative cases (6.26 ± 2.06 IU/L) but the difference was not statistically significant ($p > 0.20$).

Table 1. Comparison of CSF ADA levels in different groups

Group	No. of cases	CSF ADA level IU/L		
		Mean	SD	Range
A Tuberculous meningitis	29	6.43	1.93	3.33-9.84
B Pyogenic meningitis	15	1.89	0.91	0.48-4.44
C Aseptic meningitis	12	0.90	0.45	0-1.44
D Controls	20	0.64	0.57	0-1.55

A vs B $t = 8.42$, d.f. = 42, $p < 0.001$
 A vs C $t = 9.57$, d.f. = 39, $p < 0.001$
 A vs D $t = 12.76$, d.f. = 47, $p < 0.001$

Table 2. CSF ADA level in tuberculous meningitis according to culture status of CSF

Group	No. of cases	CSF ADA level IU/L		
		Mean	SD	Range
CSF culture positive	6	7.43	1.24	6.28-9.50
CSF culture negative	23	6.26	2.06	3.33-9.84

Culture positive vs negative : $t = 1.28$, d.f. = 27, $p > 0.20$

Table 3 reveals the ADA values in relation to CSF proteins. The mean ADA level increased with increase in protein level. In 0-100 mg%, 101-200 mg% and more than 200 mg% protein groups, the mean ADA activity was 4.19 ± 0.52 , 6.24 ± 0.42 and 8.65 ± 0.78 IU/L respectively. The increase in mean ADA level was statistically significant. However, there was no significant difference in the mean ADA value according to CSF sugar level (Table 4). Table 5 shows mean ADA value in relation to CSF lymphocyte count ratio in tuberculous meningitis. In 0-50, 51-70, 71-

Table 3. CSF ADA levels in tuberculous meningitis according to CSF proteins

Protein (mg %)	Noofcases	CSF ADA level IU/L		
		Mean	SD	Range
A 0-100	9	4.19	0.52	3.33-4.80
B 101-200	10	6.24	0.42	5.31-6.66
C More than 200	10	8.65	0.78	7.41-9.84

A vs B $t = 8.97$, d.f. = 17, $p < 0.001$. A vs C $t = 13.68$, d.f. = 17, $p < 0.001$. Bvs C $t = 8.09$, d.f. = 18, $p < 0.001$.

Table 4. CSF ADA level in tuberculosis meningitis according to CSF sugar

CSF sugar (mg %)	No. of cases	CSF ADA level IU/L		
		Mean	SD	Range
Less than 40	24	6.00	2.21	3.33-9.84
More than 40	5	7.60	1.48	6.66-9.50

t = 1.49, d.f. = 27, p > 0.10

Table 5. CSF ADA level in tuberculous meningitis according to CSF lymphocyte counts

Count (%)	No. of cases	CSF ADA level IU/L		
		Mean	SD	Range
0-50	2	3.82	0.70	3.33-4.32
51-70	4	4.06	0.49	3.33-4.39
71-90	12	5.83	0.84	4.44-6.66
91-100	11	8.43	1.04	6.24-9.84

0-70 vs 71-90% t = 4.58, d.f. = 16, p < 0.001

0-70 vs 91-100% t = 9.09, d.f. = 15, p < 0.001

71-90 vs 91-100% t = 6.33, d.f. = 21, p < 0.001.

90 and 91-100% lymphocyte count groups, mean ADA levels were 3.82 ± 0.70 , 4.06 ± 0.49 , 5.83 ± 0.84 and 8.43 ± 1.04 IU/L respectively. A statistically significant correlation was found (p < 0.001)

In none of the 29 cases with tuberculous meningitis, was CSF ADA found to be less than 3.30 IU/L while one in only of the 27 non-tuberculous cases was it higher than 3.30 IU/L. On the basis of these results, the sensitivity of adenosine deaminase activity test for diagnosis of tuberculous meningitis was 100% and specificity 97.87%.

Discussion

There is considerable urgency in establishing the correct diagnosis of tuberculosis in patients with meningitis because specific therapy is most effective when instituted early in the course of illness. Irreversible brain damage may result while waiting for culture to confirm the diagnosis. Symptoms, results of biochemical, microscopic and bacteriological examination are

seldom conclusive. Thus it is usual to begin specific therapy for tuberculosis on the basis of a presumptive clinical diagnosis.

The results of this study seem to confirm the usefulness of the adenosine deaminase test for timely and early diagnosis of tuberculous meningitis. Adenosine deaminase level was clearly higher in the patients with tuberculous meningitis. By using 3.3 IU/L as the cut off value, the test has sensitivity of 100% and a specificity of 97.87% in this series.

The mean ADA levels in CSF in cases with tuberculous meningitis have been reported to be higher (11.7 - 15.7 IU/L) by other workers.^{1,7,8,9} The lower mean ADA activity in our study may be because of the racial differences or difference in the method of estimation of ADA values.

There was no statistical difference in the CSF ADA levels in culture positive and culture negative tuberculous meningitis cases. The CSF sugar levels also did not produce any significant difference. However, when the increase in the mean CSF ADA level with the increase in CSF protein level was compared, it was found statistically significant. CSF ADA value also increased with the increase in lymphocyte count in CSF. It is, therefore, evident that determining ADA level in the CSF is a simple and very useful test for the early diagnosis of tuberculous meningitis.

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