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Dr. Mohd Ashraf Ul Abeddin
Associate Professors, Department of General Medicine, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

Dr. Akash Choudary
Associate Professors, Department of General Medicine, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

Corresponding Author:
Dr. Akash Choudary
Associate Professors, Department of General Medicine, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

A study on adenosine deaminase (ADA) levels in tubercular meningitis

Dr. Mohd Ashraf Ul Abeddin and Dr. Akash Choudary

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Abstract
Tubercular meningitis is a type of septic meningitis is a significant cause of morbidity and mortality in developing countries like India due to lack of early and timely diagnosis case fatality remains higher. Even when not fatal, the sequels are distressing and disabling.
Cerebrospinal fluid (CSF) evaluation is single most important aspect of lab diagnosis in meningitis, Analysis of CSF abnormalities to a great deal facilitates the diagnosis and initial therapy. Basic studies of CSF includes measure of pressure, cell count, cell types and estimation of glucose, protein and chloride levels and also grams staining and culture.
The definitive diagnosis of tubercular meningitis depends on detection of acid-fast bacilli (AFB) and culture of mycobacterium tuberculosis from CSF specimen but AFB is seen on direct smear of CSF sediment in only 20% of cases and it takes 4-8 weeks to be grown in culture. Hence there is a need for test like levels of Adenosine deaminase (ADA) for assistance in diagnosis of tubercular meningitis and to differentiate it from other causes of meningitis.
Materials and Methods: Minimum 100 patients, both male and female with symptoms suggestive of meningitis over a period of 1 and half years, admitted SIMS, Hyderabad were included in this study and the following investigations were done.
It was clinical cross sectional study of 25 cases of Tuberculosis, 25 cases of pyogenic meningitis and 25 cases of aseptic meningitis. 25 controls with age and sex matched individuals without evidence of any neurological diseases served as control for CSF ADA. Study was conducted to evaluate the usefulness of levels of ADA in diagnosis of tubercular meningitis and to compare the levels of ADA in different types of meningitis for early and rapid diagnosis of meningitis.
Results: In this study of 100 patients, 25 (100%) patients of the tubercular group had CSF ADA levels of more than 10 IU/dL with a mean of 13.68 IU/dL with 80% of the patients having ADA levels between 11 and 15 IU/dL. Mean ADA levels of aseptic meningitis was 8.00 IU/dL, pyogenic was 5.76 IU/dL and control group had mean ADA of 2.12 IU/dL.
Conclusion: All patients with tubercuolous meningitis had elevated CSF ADA activity. CSF ADA activity in tuberculous meningitis was significantly higher when compared to pyogenic meningitis, aseptic meningitis and controls. Elevated levels of CSF ADA had very high sensitivity and specificity in diagnosis of tuberculous meningitis. Estimation of CSF ADA is a simple, cheap, rapid, and fairly specific method that helps in early diagnosis of tuberculous meningitis and can be included in the routine investigation of tuberculous meningitis.

Keywords: ADA (Adenosine deaminase) TBM, *Pyogenic meningitis*, *Aseptic meningitis*

Introduction
Tuberculous meningitis is a cause of significant morbidity and mortality in developing countries like India. With the onset of HIV pandemic, the incidence of tuberculous meningitis is increasing even in western countries. Due to lack of early and timely diagnosis of tuberculous meningitis, case fatality rate remains high. Even when it is not fatal, the sequelae are distressing and disabling [2].
Cerebrospinal fluid (CSF) evaluation is the single most important aspect of laboratory diagnosis of meningitis. Analysis of CSF abnormalities to a great deal facilitates the diagnosis and influences the initial therapy. Basic studies of CSF that should be performed in meningitis include, measurement, of pressure, cell count and differential count, estimation of glucose and protein levels, Gram's stain and culture [1, 2].
The definitive diagnosis of tuberculous meningitis depends on the detection of acid fast bacilli (AFB) and culture of M.tuberculosis from CSF. AFB is seen on direct smear of CSF sediment in only 20% of the cases.

However, it takes 4-8 weeks for the bacilli to be grown in culture. Even the characteristic CSF cytological and biochemical changes is also variable and be even absent [3]. Hence there is a need for a simple, rapid, accurate and specific test to confirm the diagnosis of tuberculous meningitis [3].

Adenosine deaminase (ADA) is an enzyme of purine catabolism leading to hydrolytic deamination of adenosine to inosine and ammonia. ADA is secreted by T lymphocytes and macrophages during infections. Therefore, ADA estimation has shown promising results in the diagnosis of tuberculous pleural, peritoneal, pericardial effusions and tuberculous meningitis [3].

There are several forms of ADA but the prominent once are ADA1 & ADA2. ADA1 isoenzyme is found in all cells, with highest concentration founds in lymphocytes and monocyte, where as ADA2 isoenzyme is found only in monocytes. The ADA2, is the predominant form TB fluid. ADA1 & ADA2 ratio less than 0.45 is high suggests of TB.

In the present study, we have made an attempt for early diagnosis of tuberculous meningitis by estimating ADA activity in CSF.

Objectives

1. To evaluate the diagnostic significance of cerebrospinal fluid (CSF) adenosine deaminase (ADA) activity in tuberculous meningitis.
2. To compare the values of cerebrospinal fluid (CSF) ADA in different types of meningitis and with that of controls.

Materials and methods

The present study was conducted in SIMS Hyderabad, during the period November 2018 to October 209.

In the present clinical cross sectional study, 25 cases of tuberculous meningitis, .25 cases of pyogenic meningitis, 25 cases of aseptic meningitis and 25 controls were included. Age and sex matched individuals without evidence of any neurological disease served as controls for CSF ADA assay (individual subjected to elective surgery under spinal anesthesia).

Cases of tuberculous meningitis, pyogenic meningitis and aseptic meningitis were diagnosed on the basis of diagnostic criteria.

Diagnostic Criteria for Pyogenic Meningitis [63]

Clinical features suggestive of pyogenic meningitis.

A. Laboratory criteria

1. Gram's staining of CSF allowing identification of causative microorganism.
2. Positive CSF bacterial culture.
3. Classic CSF abnormalities:

a) Polymorphonuclear leukocytosis (>100cells/microliter)
b) Decreased glucose concentration (<40mg/dl)
c) Increased protein concentration (>45mg/dl)
d) Increased opening pressure.

Diagnosis of pyogenic meningitis was made on the basis of clinical features supported by atleast one of the laboratory criteria.

Inclusion Criteria

Clinical features and CSF analysis suggesting a diagnosis of tuberculous, pyogenic and aseptic meningitis.

Exclusion Criteria

1. Meningitis due to other etiologies, cerebrovascular accidents and space occupying lesions.
2. Those who have already received specific therapy before.
3. HIV infected patients.

After selection, detailed history and clinical examination was done as per the predesigned proforma. In history and examination, special emphasis was given to detect the presence of extra meningeal tuberculosis and predisposing factors. Routine laboratory tests like haemoglobin, complete blood count, ESR, blood chemistry were done in all the cases. Chest X-Ray was obtained in most of the cases. Sputum in available cases was sent for AFB smear, Gram's stain and culture. In cases of meningitis associated with otitis media, ear discharge was sent for Gram's stain and culture.

Lumbar puncture was done with full aseptic precautions and CSF was sent for biochemical (sugar and protein), cytological (cell type and count), bacteriological (AFB smear and culture, Gram's stain and culture) and Adenosine deaminase estimation. Cryptococcal meningitis was ruled out by India ink staining.

Results

Age incidence

Table 1: Age incidence of tuberculous meningitis

Age groups (in years)	No.of cases	Percentage
< 20	4	16
21-30	8	32
31-40	10	40
41-50	1	4
51-60	2	8
Total	**25**	**100**

The age of patients with tuberculous meningitis varied from 18 to 52 years with a mean of 31.04. The majority of patients were in the age group of 31-40 years (40% of the cases).

Sex Incidence

Table 2: Sex incidence in tuberculous meningitis.

Sex	No.of cases	Percentage
Male	14	56
Female	11	44
Total	**25**	**100**

The incidence of tuberculous meningitis was more common in males compared to females with male: female ratio of 1.4:1.

Presenting Complaints

Table 3: Spectrum of symptoms in TBM

Symptoms	No.of cases	Percentage
Fever	22	88
Headache	20	80
Altered sensorium	18	72
Vomiting	16	64
Seziures	7	28
Focal deficits	4	16

Signs of Meningeal Irritation

Table 4: Incidence of meningeal irritation in TBM.

Sign	No. of patients	Percentage
Neck rigidity	21	84
Kernig's sign	14	56
Brudzinski's sign	2	8

Papilloedema

4 Cases (16%) of tuberculous meningitis had papilloedema.

Cranial Nerve Palsies

Table 5: Incidence of cranial nerve palsies in TBM.

Cranial nerves		No. of patients	Percentage
Oculomotor nerve		1	4
Abducent nerve	Unilateral	2	8
	Bilateral	1	4
Trochlear nerve		1	4
Facial nerve	UMN	1	4
	LMN	1	4
Other cranial nerves		0	0

Cranial nerve palsies were more common in tuberculous meningitis (28% of the cases). Commonest cranial nerve involved was abducent nerve followed by facial nerve.

Motor Deficits

Table 6: Incidence of motor deficits in TBM

Neurological deficits	No. of patients	Percentage
Monoplegia	Nil	0
Hemiplegia	4	16
Paraplegia	Nil	0

Four Patients (16%) had hemiparesis rest of the patients were normal.

CSF Analysis

Appearance of CSF

Table 7: CSF appearance in TBM

CSF Appearance	No. of patients	Percentage
Clear	6	24
Opalescent	15	60
Turbid	4	16

The majority of patients with tuberculous meningitis had opalescent CSF (60%), whereas only 6 patients had clear CSF.

Table 8: Protein in CSF

Protein (mg%)	Tubercular meningitis n(%)	Pyogenic n(%)	Aseptic n(%)	Total n(%)
20-40	0	0	13 (52%)	13 (17.30%)
41-70	10 (40%)	13 (52%)	8 (32%)	31 (41.30%)
71-100	9 (36%)	12 (48%)	3 (12%)	24 (32%)
>100	6 (24%)	0	1 (4%)	7 (9.30%)
Total	**25 (100%)**	**25 (100%)**	**25 (100%)**	**75 (100%)**

Table 9: Sugar level in CSF

Sugar level in CSF (mg%)	Tubercular meningitis n(%)	Pyogenic n(%)	Aseptic n(%)	Total n(%)
<50	10 (40%)	20 (80%)	7 (28%)	37 (49.30%)
51-100	14 (56%)	5 (20%)	17 (68%)	36 (48%)
>100	1 (4%)	0	1 (4%)	2 (2.70%)
Total	**25 (100%)**	**25 (100%)**	**25 (100%)**	**75 (100%)**

Table 10: Lymphocyte count in CSF

Lymphocyte count (per cumm)	Tubercular meningitis n(%)	Pyogenic n(%)	Aseptic n(%)	Total n(%)
<30	0	25 (100%)	25 (100%)	50 (66.70%)
31-60	10 (40%)	0	0	10 (13.30%)
61-90	10 (40%)	0	0	10 (13.30%)
>90	5 (20%)	0	0	5 (6.70%)
Total	**25 (100%)**	**25 (100%)**	**25 (100%)**	**75 (100%)**

Other tests

Most of the patients with tuberculous meningitis and total blood count within normal limits.

Majority of patients with tuberculous meningitis had elevated ESR (>30mm/hour). The majority of patients with tuberculous meningitis had hemooglobin value more than 10gm/dl while some cases had haemoglobin value less than 10gm/dl.

Chest X-ray

In the present study, chest x-ray was obtained in 25 patients. Evidence of tuberculosis was found in 6 patients (24% of the cases) and was normal in 19 patients.

CT Scan Brain

CT scan brain was obtained in 25 cases of tuberculous meningitis. 4 cases had basal exudates, 5 cases had cerebral edema. One case had right middle cerebral artery infarction. 2 patients had tuberculoma, while the other 13 patients had normal CT Scan.

Table 11: ADA in CSF

ADA in IU/dL	Tubercular meningitis n(%)	Pyogenic n(%)	Aseptic n(%)	Control n(%)
1-5	0	14 (56%)	0	25 (100%)
6-10	0	11 (44%)	25 (100%)	0
11-15	20 (80%)	0	0	0
16-20	5 (20%)	0	0	0
Total	**25 (100%)**	**25 (100%)**	**25 (100%)**	**25 (100%)**

Table 12: Mean ± SD and Range of CSF ADA activity in different groups.

	Total No. of cases	CSF – ADA levels in IU/dL		
		Mean	SD	Range
Tuberculous meningitis	25	13.68	±2.21	11-19
Pyogenic meningitis	25	5.76	±2.18	3-10
Aseptic meningitis	25	8.00	±1.32	6-10
Controls	25	2.12	±1.13	1-4

The mean CSF ADA activity was highest in tuberculous meningitis compared to other groups.

Table 13: Showing diagnostic efficacy of CSF ADA in TBM using 10.0 u/l as cut off value.

Test	TBM Vs Controls	TBM Vs Non-tuberculous meningitis (pyogenic and aseptic meningitis)
Sensitivity	100%	100%
Specificity	100%	92%
Positive Predictive Value	100%	86%
Negative predictive	100%	100%
Efficiency of test	100%	95%

Discussion

Tuberculosis continues to be a major health problem of developing countries like India. Neurotuberculosis is the most dreaded complication. Tuberculous meningitis is the commonest manifestation of neurotuberculosis.

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. Irreverisble brain damage may result while waiting for culture to confirm the diagnosis. Therefore, determining ADA level in CSF can be a simple and very useful test for early diagnosis of tuberculous meningitis.

Age Distribution

Tuberculous meningitis can occur in any age group, but is common in young children. In the present study, age of patients ranged from 18 years to 52 years and mean age was 31.04 years. Majorities of patients were in 3rd decade. The observations of present study correlate with that of Kent *et al*[1] (mean age: 31 years) and Srivatsa *et al*. [2] (maximum incidence: 21-30 years).

Sex Distribution

In the present study, out of 25 patients of tuberculous meningitis 14 were males and 11 were females, with male to female ration of 1.4:1. The observations of our study correlate with that of Vimla Virmani *et al*. [3] (male: female ration = 1.398:1).

Signs of Meningeal Irritation

In the present study, signs of meningeal irritation were present in all but two patients (92% of cases). Neck rigidity was present in 21 cases (84%), Kernig's sign was present in 14 cases (56%) and Brudzinski's sign was present in 2 cases (8%). The present study correlates with that of Kennedy *et al*. [4]

Fundal Changes

In the present study, fundoscopic examination revealed papilloedema (or incipient papilloedema) in 4 patients (16% of cases). Choroid tubercles were not seen in any of the patients that of Srivatsa *et al*. [2] (22.2%).

1. Cranial Nerve Palsies

Paresis of cranial nerves (ocular nerves in particular) is frequent finding in TBM. In the present study 8 cases (28%) had cranial nerve palsies. The results of the present study correlates with that of Verdon *et al*. [5] (31.25%).

In the present study, occulomotor nerve palsy was observed in 1 patient (4%). Vimla Virmani *et al*. [3] (4%) and Thomas *et al*. [6] (6.03%) made similar observations. Trochlear nerve palsy was observed in one patient (4%), similar observations were made by Thomas *et al*. [72] (3.44%). Abducent nerve palsy was observed in 3 patients (12%), similar observations were made by Thomas *et al*. [6] (18%). In the present study, facial nerve palsy was observed in 2 patients (6%).

2. Focal Deficits

Focal neurological deficits and common in TBM and they may precede signs of meningeal irritation. In the present study, focal motor deficits in the form of hemiplegia were observed in 4 patients (16%). Similar observations with regard to hemiplegia were made by Traub *et al*. [7] (12.5%), Thomas *et al*. [72] (18.53%) and Mohopatra *et al*. [8] (13.3%).

CSF analysis in Meningitis

3. CSF Appearance

In the present study, CSF was clear in 6 cases (24%).Similar observations were made by Singh R.G. *et al*[9] (16.69%).

4. Lymphocytes in CSF

In the present study all the patient with TBM had lymphocyte predominance in CSF with mean value of 75.12 cells/cumm with 40% of the people having lymphocytes ranging 60-90.

The present study correlate with Swart *et al*. [61] had lymphocytic predominance in 87.5% patients, Traub *et al*. [7] (100%).

Neutrophils in CSF

Neutrophilic predominance seen in pyogenic meningitis with mean value of 70.12 cells/cumm with 17 (68%) of patients having neutroplhils >60 cells/cumm.

5. CSF Protein

In the present study, CSF Protein was elevated in all cases. The mean CSF protein was 78.24 mg/dl and ranged from 41-130 mg/dl. Similar observations were made by Swart *et al*. [10]

In the present study, 6 cases (24%) had CSF protein between >100. Similar observations made by Mohapatra *et al*. [8] (36.67%)

CSF Glucose

In the present study, CSF glucose ranged from 30 to 130 mg/dl with a mean of 57.9mg/dl. 40% of patients had CSF glucose values less than 50mg/dl and 14 patients had 51-100mg/dl.

In the present study, CSF ADA level of 10 U/L was used as cut off value for diagnosis tuberculous meningitis, as all the patients with TBM had the level more than 10. Sensitivity of the test was 100% and specificity was also 100%, when TBM was compared to controls. When TBM was compared to non- tuberculous meningitis group (pyogenic and aseptic meningitis), the sensitivity and specificity were 100% and 92% respectively.

Conclusion

- All patients with tubercuolous meningitis had elevated CSF ADA activity.
- CSF ADA activity in tuberculous meningitis was significantly higher ($P<0.05$) when compared to pyogenic meningitis, aseptic meningitis and controls.
- Elevated levels of CSF ADA had very high sensitivity and specificity in diagnosis of tuberculous meningitis.
- Estimation of CSF ADA is a simple, cheap, rapid, and fairly specific method that helps in early diagnosis of tuberculous meningitis and can be included in the routine investigation of tuberculous meningitis.

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