Research Article

Analysis of cerebrospinal fluid adenosine deaminase levels in meningitis

Vyankatesh T. Anchinmane*, Shilpa V. Sankhe

Department of Pathology, B.K.L. Walawalkar Rural Medical College, Sawarde, Chiplun, Ratnagiri, India

*Correspondence:
Dr. Vyankatesh T. Anchinmane,
E-mail: a.vyankatesh@rediffmail.com

ABSTRACT

Background: A precise etiological diagnosis of meningitis is required so that appropriate therapy can be started at the earliest. Due to inconsistent clinical presentations and the lack of a rapid, sensitive and specific test, tuberculous meningitis (TBM) is particularly difficult to diagnose. The present study was done to analyze the utility of adenosine deaminase (ADA) activity in CSF for differentiating TBM from other forms of meningitis.
Methods: In our study, ADA activity measured in 26 TBM, 15 pyogenic meningitis (PM) and 10 aseptic/viral meningitis (AM) cases. A cut-off ADA level of 10 IU/L was used for differentiation of TBM cases from other meningitis cases.
Results: The mean ADA levels in CSF were highest in TBM patients as compared to PM and AM. The sensitivity, specificity and accuracy of ADA were 96.15%, 92% and 94.11% respectively for detection TBM cases from non-tuberculous meningitis cases.
Conclusions: Since ADA test is simple, rapid and inexpensive, it can be used as rapid diagnostic test for differential diagnosis of CSF and confirmation of TBM cases.

Keywords: Meningitis, Adenosine deaminase, Tuberculous meningitis

INTRODUCTION

Tuberculous meningitis (TBM) is an endemic disease in both developing and developed countries.[1] The conventional microscopy and culture are widely used however smear microscopy is sensitive in upto 20% tuberculosis confirmed cases and the culture takes up to 4 to 6 weeks to provide a result which limits the value of these methods in immediate decisions for diagnosis and treatment.[2,3]

Many tests have been suggested for the diagnosis of TBM, including the bromide partition test, the adenosine deaminase assay, latex particle agglutination, high-pressure liquid chromatography, PCR and enzyme-linked immuno-sorbent assay (ELISA) based tests.[2] The aim of the present study was to compare CSF ADA activity in different forms of meningitis and to emphasize its importance in differential diagnosis of TBM.

METHODS

CSF was taken from a total of 51 patients treated and followed up with the diagnosis of meningitis, admitted in the tertiary care hospital, who were included in the study. CSF obtained in the laboratory was divided into three groups, TBM, PM and AM. CSF adenosine deaminase activity was measured by using spectrophotometer at optimum wave length of 628 mm (620 mm-650 mm) as per method described by Giusti.[4]

Diagnosis of TBM was based on the following features

subacute or chronic outset and slow clinical progress, CSF WBC counts >50/mm^3 and lymphocytic predominance, CSF protein >40 mg% and CSF glucose less than half of blood glucose obtained simultaneously, observation of tuberculosis bacilli in ZN staining of CSF, isolation of bacteria in CSF culture and response to anti-tuberculous treatment.

Diagnosis of PM was made on the basis of the following characteristics

Acute onset and rapid clinical progress, CSF WBC count >100/mm^3 and neutrophil predominance, CSF protein >40 mg% and CSF glucose less than half of blood glucose obtained simultaneously, observation of bacteria in CSF gram staining or growth of pathogen in culture and response to antimicrobial treatment.

Diagnosis of AM was based on the following features

Acute onset, insidious and slow clinical progress, CSF WBC count >100/mm^3 and lymphocytic predominance, CSF protein close to normal, CSF glucose normal or slightly reduced, negative results in microbiological evaluation of CSF and serum for PM and TBM and full response to symptomatic treatment without antimicrobials.[4]

Statistical analysis was performed by SPSS (version 11.5) software for calculation of mean, standard deviation, sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of CSF ADA level.

RESULTS

Out of 51 patients included in the study, there were 26 TBM, 15 PM and 10 AM cases. Age range of patients was 18-55 years. The range of ADA was 9.2 to 17.5 IU/L in TBM with a mean of 14.04 IU/L and 1.90 IU/L standard deviation. While the range between 3.7 to 10.2 IU/L with mean of 5.34 IU/L and standard deviation of 2.03 IU/L was noted with PM. Similarly range of ADA between 1.3 to 4.8 IU/L with 3.3 IU/L mean and 1.1 IU/L standard deviation were observed with AM (Table 1).

Table 1: CSF ADA level in different group.

Study group	Range of ADA (IU/L)	Mean	S.D.
Tuberculous meningitis (TM) n= 26	9.2 - 17.5	14.04	1.90
Pyogenic meningitis (PM) n= 15	3.7 – 10.2	5.34	2.03
Aseptic meningitis (AM) n= 10	1.3 – 4.8	3.30	1.10

CSF ADA level 10 IU/L as a cut-off value test exhibited a sensitivity, specificity, accuracy, PPV and NPV of 96.15%, 92%, 94.11%, 92.59% and 95.83% in differentiating tuberculous from non-tuberculous meningitis (Table 2).

Table 2: CSF ADA efficacy with cut- off value of 10 iu/l.

CSF- ADA level (IU/L)	TBM cases	Non-TBM cases		Sen.	Speci.	Accu.	PPV	NPV
		PM	AM					
> 10	25	02	00	96.15%	92%	94.11%	92.59%	95.83%
< 10	01	13	10					

(Sen. = Sensitivity, Speci. = Specificity, Accu. = Accuracy, PPV= Positive Predictive Value, NPV= Negative Predictive Value).

DISCUSSION

TBM still remains as a major global health problem. The presentations may be diverse and rarely fit a standard clinical picture of TBM symptoms. The importance of this disease has increased since there is emergence of acquired immuno-deficiency syndrome (AIDS) and multidrug resistant tuberculosis (TB).[3-5]

Any delays in diagnosis and initiating the correct drug regime can lead to increased neurological complications and mortality rates which may be seen in 20-25% of cases. Hence, diagnosis is made on assessment of clinical presentation, cerebrospinal fluid (CSF) biochemistry, microscopy and evidence of present or prior TB.[6] However, routine CSF laboratory parameters may not be helpful to differentiate TBM from other meningitis like PM and AM as identification or isolation of acid-fast bacilli on CSF smear or culture is usually difficult.[7]

The tests like ZN staining for AFB bacilli, culture, PCR, ELISA have been suggested for the detection of TBM cases. The PCR is the most rapid and sensitive diagnostic test compared to the other methods, however, it requires a relatively large volume of CSF, dedicated laboratory and rigorous quality control to maintain accuracy. Hence, CSF PCR not used as a screening procedure, in view of, high cost of test and large volume of CSF required.[2]

CSF ADA levels are known to be raised in TBM cases and their use has been suggested to help differentiate TBM from other forms of meningitis like AM and PM. Adenosine deaminase is an enzyme required for lymphocyte proliferation and differentiation. The ADA enzyme activity is known to be elevated in certain infection where cell mediated immunity plays role. ADA level increases in CSF due to the damaged blood brain barrier which permits ADA to enter into CSF from the

blood or adjacent cerebral tissue. ADA level also increases as a result of lymphocytic proliferation indicating local immune response. It is also thought that ADA enzyme is released in CSF by T lymphocytes during cell mediated immune (CMI) response to tuberculous infection.[3,4]

In the present study, the mean CSF ADA activity (14.04 TU/L) in TBM cases was significantly elevated as compared to PM (5.34 IU/L) and AM (3.30 IU/L). In the present study, CSF ADA level 10 IU/L as a cut-off value exhibited a sensitivity, specificity and accuracy of 96.15%, 92% and 94.11% respectively for the diagnosis of TBM cases from non-TBM cases (PM and AM cases).

In this study, it is observed that there was statistically significant difference in the CSF ADA levels of TBM and other groups of meningitis and no significant difference were observed in the CSF ADA levels in differentiating between PM and AM, however the former can easily be differentiated by CSF cytochemical analysis.

Results of our study indicate that ADA levels in CSF are of great value in diagnosis of TBM and in differentiating TBM from other meningitis i.e. PM and AM. Similar findings were also observed by various authors in the past. Shariff MH et al, Nethala SV et al and Ramakrishana MR et al also observed that CSF ADA level (cut off 10U/L) is best parameter to differentiate TBM from AM and PM.[3,4,8]

Levels of ADA in CSF of TBM have been evaluated in few earlier studies which showed that raised levels of ADA in CSF may not be specific to meningitis and are also raised levels in other conditions like intracranial tumors. Hence, results should always be correlated with clinical findings.[2,9]

In view of such observations, the present study presented the usefulness of CSF ADA test in differentiating PM and AM cases from cases of TBM.

CONCLUSION

ADA estimation in CSF is a rapid, reliable, cost-effective and fairly sensitive and specific test for helping a clinician in making early diagnosis and treatment of TBM and also to prevent fatal and morbid complications of TBM when confronted with a dilemma of differential diagnosis of TBM and other meningitis. Hence, CSF ADA estimation in meningitis patients should find a place in routine laboratory methodology.

REFERENCES

1. Mastroianni CM, Paolotti F, Lichtrer MD, Agostino C, Vullo V, Delia S. Cerebrospinal fluid cytokines in patients with tuberculous meningitis. Clinical Immunopathology. 1997;84:171-6.
2. Caws M, Wilson SM, Clough C, Drobniewski F. Role of IS6110-targeted PCR, culture, biochemical, clinical, and immunological criteria for diagnosis of tuberculous meningitis. J Clinical Micro. 2000;38(9):3150-5.
3. Shariff MH, Vidya P. Cerebrospinal fluid adenosine deaminase activity in tuberculous meningitis cases. Search Results. Int J Pharma Bio Sci. 2014;4(1):95-8.
4. Nethala SV, Anke G. Adenosine deaminase levels in cerebrospinal fluid among tubercular meningitis patients. 2015;3(11):914-8.
5. Thweites G, Chan TTH, Mai NTH. Tuberculous meningitis. J Neurol Neurosurg Psychait. 2000;68:289-99.
6. Kennedy DH, Fallon RJ. Tuberculosis meningitis. J Am Med Asso. 1979;241:264-8.
7. Molavi A, Le FJL. Tuberculous meningitis. Med Clinics North Am. 1985;69:315-31.
8. Ramakrishna MR, Trupti RR, Shrinivasa Rao K, Shrinivas T, Bhat H. Adenosine deaminase activity in cerebrospinal fluid for diagnosis of tuberculosis meningitis. Int J Pharma Bio Sci. 2013;4(1):344-51.
9. Martinez VJM, Ocana I, Ribera E. Adenosine deaminase activity in diagnosis of tuberculous peritonitis. Gut. 1986;27:1049-53.