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Estimation of Adenosine Deaminase Levels in CSF in Different Etiology of Meningitis

Anshul Bhateja[1], Gurpreet Singh[2], Akriti[3], Manpreet Kaur[4]

[1]Junior Resident, Department of Medicine, Government Medical College, Amritsar, [2]Medical Officer Specialist, CHC, Fategarh Churian, Amritsar, [3]Department of Pathology, Christian Medical College, Ludhiana, [4]Medical officer, PHC, Othian.

Abstract

Background: Meningitis is the most common sequelae to microbial invasion of the CNS and is more common in the developing countries than developed countries. Its Neurological sequalae are serious and rather common among survivors. **Aim:** To assess the difference in ADA activity in CSF in different types of meningitis and to differentiate between various etiologies of meningitis including pyogenic, tuberculous and viral meningitis using ADA levels in CSF. **Subjects and Methods:** The study included fifty patients (n=50) of meningitis, admitted in emergency, indoor medical wards and ICU of Guru Nanak Dev Hospital, Amritsar. The CSF specimens were obtained by lumbar puncture using all the aseptic precautions. CSF ADA was recorded by Giusti and Galantimethod. **Results:** Mean ADA levels in TBM was 19.09±8.16 IU/l, In pyogenic meningitis was3.9- 6.39±1.26 IU/l while in viral meningitis was 6.57±1.30 IU/l. On comparison, CSF ADA was found to be markedly raised in TB meningitis, while lower ADA values are seen in PM and VM. **Conclusion:** It can be concluded that ADA estimation in CSF is inexpensive and rapid anda reliable method for diagnosis of tuberculousetiology in TBM as CSF ADA levels are is markedly raised in tubercular meningitis, while lower ADA values are seen in pyogenic meningitis and viral meningitis.

Keywords: Adenosine deaminase; Tuberculous meningitis; viral meningitis; pyogenic meningitis.

Corresponding Author: Dr. Gurpreet Singh, Medical Officer Specialist, CHC, Fategarh Churian, Amritsar.

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Introduction

The central nervous system (CNS) may appear protected from the external environment by a blood brain barrier – a system of tight junction around capillaries that resist the entry of pathogens, inflammatory cells and macromolecules into the subarachnoid space and the brain. However, the barrier fails to resist the invasion of the microbes and its presence also causes difficulty in the delivery of antimicrobial agents in adequate concentration.

Meningitis is the most common sequelae to microbial invasion of the CNS and is more common in the developing countries than developed countries. Its Neurological sequalae are serious and rather common among survivors.[1] Acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess, subdural empyema and infectious thrombophlebitis are distinct clinical presentations.[2] The early diagnosis and treatment remains a challenge to the clinician.The classic triad of diagnostic signs consists of nuchal rigidity, sudden high fever, and altered mental status; however, all the three features are present in only 44–46% of bacterial meningitis cases.[3,4]

In tuberculous meningitis, the early manifestations are usually low-grade fever, malaise, headache (more than 50 percent of cases), slow mentation, confusion, and neck rigidity (75 percent of cases), with Kernig and Brudzinski signs. The seeding of tuberculous bacilli into CSF leads to development of clinical picture comprising of gradually fluctuating fever, weight loss, headache, behaviour changes and vomiting. Interventional delay leads to neurological deficits, loss of consciousness, seizures and it is the most common point of time when the diagnosis of tubercular meningitis is considered. Signs of cranial nerve involvement (usually ocular palsies, less often facial palsies or deafness) and papilledema may be present in TB Meningitis.

Viral meningoencephalitis, and particularly herpes simplex virus (HSV) encephalitis, can mimic the clinical presentation of bacterial meningitis. The typical CSF profile with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, in contrast to neutrophilicpleocytosis and hypoglycorrhachia, which is characteristic of bacterial meningitis.[2]

Partially treated patients with the use of inappropriate antibiotics can obscure the cytological and biochemical status of the spinal fluid and the chance of recovery of organisms from the spinal fluid will also become less. They can also simulate the CSF picture of viral meningoencephalitis.

In Enteroviral meningitis, the polymorphs can flood the CSF in first 6 hours along with normal CSF glucose. In immunosuppressed patients, the mounting of CSF

inflammatory response is suboptimal and can also simulate the viral picture. Hence a quick and reliable method for differentiating bacterial and viral meningitis is essential for optimal management outcome.

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.[5]

Its levels are ten times higher in T-lymphocytes than in erythrocytes. The enzyme activity increases during mitogenic and antigenic responses of lymphocytes and T-lymphocyte blastogenesis can be inhibited by inhibitors of ADA. ADA is now being recognized as a marker of cell mediated immunity particularly as a marker of T lymphocyte activation. Adenosine deaminase levels (ADA) have also been considered by several researchers to differentiate tubercular disease from non-tubercular.[6-10]

Therefore the present study was undertaken to assess the difference in ADA activity in CSF in different types of meningitis and to differentiate between various etiologies of meningitis including pyogenic, tuberculous and viral meningitis using ADA levels in CSF.

Subjects and Methods

This cross-sectional study was conducted in the Department of Medicine, Guru Nanak Dev medical college and Hospital, Amritsar. The study included fifty patients (n=50) of meningitis, on the basis of clinical findings, CSF findings and MRI brain who were admitted to the emergency and ICU of the hospital.All those Patients who were diagnosed with meningitis and meningo-encephalitis were included in the study. While Patients of meningitis less than 14 years of age, with CVA/ stroke, with cirrhotic encephalopathy, those with uremic encephalopathy, with hypoxic ischemic encephalopathy and toxic-metabolic encephalopathy were excluded from our study.Information regarding their age, sex and clinical diagnosis was collected. Biochemical testing was performed in the department of Biochemistry of Govt. Medical College, Amritsar.This study was undertaken after approval of the Institutional Ethics Committee, Government Medical College, Amritsar. A Written informed consent of the patients was obtained in vernacular language for their inclusion.

All patients had undergone complete clinical examination of blood pressure, pulse rate and systemic examination, including detailed neurological examination. Meningitis patients were screened for the various biochemical and radiological parameters like CBC,CSF complete examination,CSF culture,Serum Electrolytes,Serum creatinine,Blood urea,Liver function tests and CSF adenosine deaminase levels.

Collection of CSF sample:

The CSF specimens were obtained by lumbar puncture using all the aseptic precautions; The following procedures were routinely performed on all CSF specimens: Protein, Glucose (Glucose Analyser), Analysis for total and differential leucocyte count and Gram stain, and culture on blood agar and heated blood agar. Chest X-ray, and ultrasound abdomen were done, when indicated.

Complete clinical examination and proper detailed history of all the meningitis patients admitted in medical wards was recorded, at the time of admission. Finally, the clinical evaluation was observed and recorded. According to the above mentioned criteria patients were diagnosed as Tuberculous, Pyogenic and Viral Meningitis.

Estimation of ADA in CSF:

We used Giusti and Galanti[11] method for detection of CSF ADA levels based on the principle that Adenosine deaminase hydrolyses adenosine to ammonia and inosine. The ammonia formed further reacts with a phenol and hypochlorite in an alkaline medium to form a blue indophenol complex with sodium nitroprusside acting as a catalyst. Intensity of the blue coloured indophenol complex formed is directly proportional to the amount of ADA present in the sample. Reference range of >10U/L was considered as positive.

STATISTICAL ANALYSIS:

The data was collected systematically and analysed statistically according to the standard statistical methods using One way analysis of variance (ANOVA) and p value <0.005 was considered as significant.

Results

A total of 50 patients were included in the study. Mean age of subjects in our study came out to be 41.6±17.1 years with majority of subjects (32%) belonging to the age group of 31-40 years.Male predominance was observed comprising of 62% males and overall, Male : female ratio in the present study observed was 1.63:1. Maximum male population was seen in age range of 21-30 years while maximum female population was seen in 41-50 and 61-70 years of age.

Further, in the present studywe included 17cases of tubercular meningitis, 16 cases of pyogenic meningitis and 17 cases of viral meningitis.ADA levels were found to be elevated (ADA ≥10 IU/l) in 100% cases in TBM, Whereas 100% cases of pyogenic meningitis (16/16 cases) and 100% cases of viral meningitis presented with ADA levels ≤10 IU/l. (Table 1, figure 1).

Table 1: Number of Cases Showing Elevated ADA Levels in Different Types of Meningitis

CSF Analysis	TBM (N=17)		PM (N=16)		VM (N=17)	
ADA Levels (IU/L)	n	%	n	%	n	%
≥10 IU/l	17	100%	0	0	0	0
≤10 IU/l	0	0	16	100%	17	100%

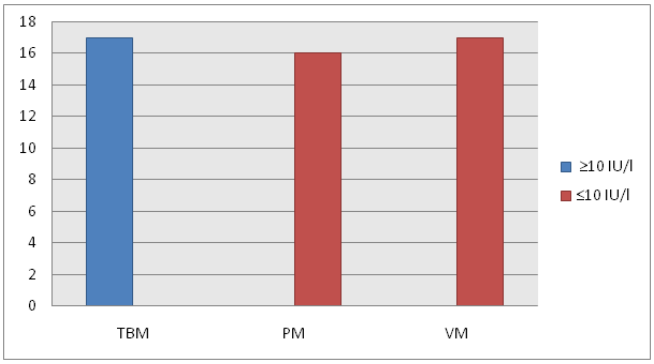

Figure 1: Number of Cases Showing Elevated ADA Levels in Different Types of Meningitis

ADA levels in different types of meningitis as observed showed that ADA levels in TBM were in the range of 11.1-35 IU/l with mean of 19.09±8.16 IU/l, In pyogenic meningitis were 3.9-8 IU/l with mean 6.39±1.26 IU/l while in viral meningitis were of 3.2-9 IU/l with mean of 6.57±1.30 IU/l. On comparison, CSF ADA was found to be markedly raised in TB meningitis, while lower ADA values are seen in PM and VM. Hence, difference between ADA values between TBM & PM and TBM & VM in both the groups is statistically significant (p<0.0001, 95% CI= 60.6095 to 107.9505). (Table 2, graph 3).

Table 2: CSF ADA Levels and Diagnosis in Different Types of Meningitis

Diagnosis	Total No of Patients	ADA Levels (IU/L)		P Value
		Min-Max	Mean	
TBM	17	11.1-35	19.09±8.16	P<0.001*
PM	16	3.9-8	6.39±1.26	
VM	17	3.2-9	6.57±1.30	

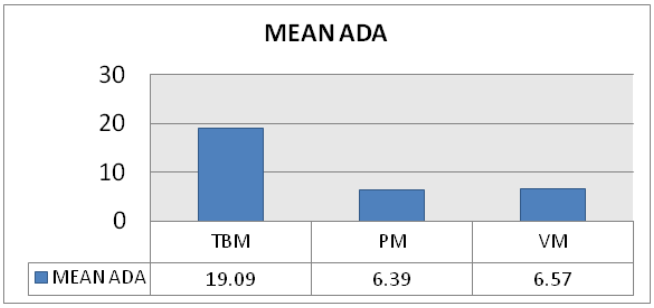

Figure 2: Mean CSF ADA Levels (IU/L) In Different Types of Meningitis in Present Study

Discussion

Estimation of CSF ADAhas been considered as a marker of cell-mediated immunity and its activity has been observed in various infections including TBM. Routine CSF laboratory findings may not be helpful to differentiate tuberculousetiology in meningitis from other causes. Considering that both humoral and cell-mediated immunity play an important role in TBM infection, it has been suggested that ADA activity in CSF may help differentiate TBM from non-TBM infectious meningitis.

Therefore in the present study we aimed to differentiate different types of meningitis o basis of etiologiesincluding pyogenic, tuberculous and viral meningitis using ADA levels in CSF.

In the present study, ADA levels were found to be elevated (ADA≥10 IU/l) in 100% cases in TBM. Whereas 100% cases of both pyogenic meningitis f viral meningitis presented with ADA levels ≤10 IU/l. ADA levels in TBM was in the range of 11.1-35 (IU/l) with mean of 19.09±8.16 while in pyogenic meningitis, it was 3.9-8 (IU/l) with mean 6.39±1.26 and in viral meningitis, it was 3.2-9 (IU/l) with mean of 6.57±1.30.The results of our study showed that on comparison, CSF ADA is markedly raised in TB meningitis, while lower ADA values are seen in Pyogenic Meningitis and Viral Meningitis. On comparison, difference between ADA values between TBM & Pyogenic Meningitis and TBM & Viral Meningitis in both the groups is statistically significant.

In accordance to our results, previous studies done by Tuon FFet al[12], Moghtaderi A et al[13]Gupta et al[14], Agarwal S[15], Gautam et al[16], Belagavi and Shalini[17] and Mehta et al[18]had shown that ADA levels were found to be significantly higher in TBM group as compared to bacterial and viral meningitis. On the contrary, Abdolbagi MH et al[19] reported that the measurement of ADA level alone is not useful as a rapid diagnostic test for TBM.

Possible explanation for raised ADA levels can be because ADA has been considered as a marker of cell-mediated immunity as it is released by T cells during cell mediated immune response (CMI) to the tubercle bacilli. Its activity has been observed in various infections including TBM. Considering that both humoral and cell-mediated immunity play an important role in TBM infection, it has been suggested that ADA activity in CSF may help differentiate TBM from non-TBM infectious meningitis.

Gupta et al[14] observed that adenosine deaminase levels in nontuberculous disease rarely exceeded the cut-off; set for tuberculous disease. They have further observed that ADA estimation is not only a fairly sensitive and specific test (more than 90 %), helpful in differentiating tubercular from non-tubercular etiology; both in pulmonary and extra-pulmonary disease but is also simple, inexpensive and rapid. For this reason this test may help in early diagnosis, improve the prognosis and reduce spread of disease and sequlae.[20]

ChanderA et al[21] reported that if the ADA assay result is negative, the probability that the patient has TBM is approximately 19%, which is not low enough to rule out TBM. Thus they suggest, that a negative ADA assay result should not be used alone as a justification to exclude or discontinue anti-TB treatment. The choice of therapeutic strategy should be based on the

results of microscopic examination of a smear or culture for Mycobacterium tuberculosis, as well as other clinical data, such as response to anti-TB treatment.

Similarly, Choi SH et al studied ADA activity in CSF of 182 patients with meningitis. The mean ADA level in tubercular group was 12.7±7.5 U/l and it was significantly higher than the other groups.[22]Chotmongkol V et al identified a CSF ADA level of 15.5U/l as the best cut-off value to differentiate tubercular meningitis and non-tubercular meningitis, with sensitivity of 75% and specificity of 93.0%.[23]

Conclusion

CSF ADA is markedly raised in tubercular meningitis, while lower ADA values are seen in pyogenic meningitis and viral meningitis. Hence, we can suggest that estimation of these enzymatic activities can be helpful in diagnosing and differentiating pyogenic, tubercular and viral meningitis.

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