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Original Research Article

Role of cerebrospinal fluid adenosine deaminase activity in the diagnosis of tuberculous meningitis in children

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ABSTRACT

Background: Early and correct treatment is essential for successful outcome in patients of tuberculous men-ingitis. Adenosine deaminase activity in the cerebrospinal fluid has been found to be a simple and useful investigation in the diagnosis of tuberculous meningitis in children.
Methods: It is a cross sectional observational hospital based study conducted at the Department of Paediatrics, Deccan College of Medical Sciences, Kanchanbagh, Hyderabad, India. Children aged 2 months to 12 years were included in the study during April 2016 to October 2016.
Results: The mean value of adenosine deaminase activity in the cerebrospinal fluid of tuberculous meningitis cases was 13.3±14.49. The mean cerebrospinal fluid adenosine deaminase levels in tuberculous meningitis patients was significantly higher than non-tuberculous meningitis patients with P <0.01.
Conclusions: The mean cerebrospinal fluid adenosine deaminase level was significantly raised in tuberculous meningitis patients.

Keywords: Adenosine deaminase, Cerebrospinal fluid, Tuberculous meningitis

INTRODUCTION

Tuberculous meningitis is the infection of the meninges caused by mycobacterium tuberculosis. India is the country with the highest burden of tuberculosis. The WHO statistics for 2015 gave an estimated incidence of 2.2 million cases of tuberculosis for India out of a global incidence of 9.6 million.[1,2] The diagnosis of tuberculous meningitis is complicated as it causes various clinical manifestations which overlap with other diseases of the central nervous system such as partially treated pyogenic meningitis and viral meningitis. Delay in diagnosis is associated with high mortality and morbidity due to sequelae.[3] Early and correct treatment is essential for a successful outcome in patients of tuberculous meningitis. Multidrug resistance further worsen the outcome of this disease.

Available methods of diagnosis of tuberculous meningitis were evaluated and were found to have low sensitivity and specificity.[4] A definitive diagnosis of tuberculous meningitis depends on the detection of acid fast bacilli in a smear and culture of Mycobacterium tuberculosis. Light microscopy has a low detection rate and cultures take a long time.[5] The characteristic cerebrospinal fluid cytological and biochemical changes are also variable with considerable overlap, there is a need for simple, sensitive, accurate and rapid tests for the diagnosis of tuberculous meningitis. A number of genotypic assays based on nucleic acid amplification have been designed.[6]

However, high costs involved in these tests prevent them to be widely used especially in developing countries. A reliable, rapid and affordable diagnostic test which can be performed in any standard pathology laboratory in resource limited settings could be of help in the diagnosis of cases of meningitis. Adenosine deaminase (ADA) is an enzyme in the purine salvage pathway that catalyses the deamination of adenosine forming inosine and ammonia in the process. The chief physiological function of ADA is related to lymphocytic proliferation and differentiation.[7]

The enzyme activity increases during mitogenic and antigenic responses of lymphocytes.[8] As a marker of cellular immunity particularly T- lymphocyte activation, activity is found to be elevated in those diseases in which there is a cell mediated immune response. Increased ADA levels have been reported in childhood tuberculous meningitis with adverse neurological outcome.[9] Likewise, deficiency of ADA is associated with severe defects in cell mediated and humoral immunity predisposing the patient to opportunistic infections. ADA levels have also been considered by several researchers to differentiate tubercular disease from non-tubercular diseases.[10,11]

METHODS

A total of fifty-five children between ages two months to twelve years admitted in the paediatrics ward during April 2016 to October 2016 at Deccan medical college were included in the present study. History taking, clinical examination and routine investigations were done and they were divided into four groups. The criteria to label a case as tuberculous included patients with history of contact with tuberculosis, clinical findings consistent with tuberculosis like fever more than two weeks duration, vomitings, convulsions, altered sensorium, cranial nerve palsies and focal neurological deficits, positive mantoux test, bacteriological proof of presence of *Mycobacterium tuberculosis*, radiological evidence of tuberculosis , CSF samples with raised protein levels and/or decreased glucose and/or pleocytosis with lymphocytic predominance. Partially treated pyogenic meningitis included patients with compatible clinical history microbiological and biochemical evidence of CSF polymorphonuclear leukocytosis, low sugar, high protein, aseptic or viral meningitis included clinically suspected patients with compatible history, CSF samples with elevated protein levels, normal sugar or pleocytosis with lymphocytic predominance. Non-infectious neurological disorders included patients with stroke, epilepsy having normal CSF biochemistry, negative culture or gram staining with no prior antibiotic therapy.

CSF samples were collected by standard lumbar puncture and stored at 4ºC. Traumatic taps or blood stained specimens were excluded from this study. CSF was subjected to biochemical and microscopic examination. ADA activity in CSF was determined at 37ºC according to the method of Guisti and Galanti based on the Berthlot reaction that is the formation of colored Indophenol complex from ammonia liberated from adenosine and quantified spectrophoto-metrically.[12]

Results are expressed as mean±SD with Range to compare the mean ADA activity between the tuberculous and non-tuberculous meningitis groups. Non-parametric anova with the Dunnett post-test was used. Cut off reference range of 10 U/L CSF ADA was taken as positive.

RESULTS

Out of fifty-five patients 32 patients fulfilled the criteria were labeled as tubercular while other 23 patients were labeled as non-tubercular. Out of 32 patients in the tubercular group 31 cases presented with fever more than two weeks duration, headache or vomiting in 17 cases, seizures in 30 cases, focal neurological deficits in 19 cases, loss of consciousness in 27 cases, abnormal movements like hemiballismus, tremors, myoclonus in 9 cases.

Table 1: mean CSF ADA levels in different study groups.

		Mean	Std.Deviation	Significance
CSF	TB meningitis	13.3250	4.49344	P < 0.01
	Pyogenicmeningtis	3.0889	1.71497	
	Viral meningitis	1.9556	0.79057	
	Non-infectious	2.0000	6.47524	

Table 2: Correlation of CSF ADA activity with other CSF parameters.

		Correlation value	Significance
CSF ADA	CSF cellcount	0.817	P < 0.05
	CSF proteins	0.819	P < 0.05
	CSF sugar	-0.206	NS

Mantoux test was positive in 9 cases, contact with TB was present in 9 cases, radiological evidence of pulmonary tuberculosis was found in 9 cases, CT brain showed hydrocephalus in 19 cases, exudates in basal cisterns in 8 cases, infarcts in 6 cases, gyral enhancement in 3 cases, evidence of tuberculoma in 4 cases.

The mean value of ADA activity in CSF of tuberculous group was 13.3±14.49. 31 cases in the tubercular group had CSF ADA levels > 10 U/L. The mean CSF ADA activity in TBM patients was significantly higher than non TBM patients with $P < 0.01$. A cut off value of 10 U/L for TBM patients gave a sensitivity of 90.62% and a specificity of 95.65% respectively. The mean CSF ADA activity had positive correlation with CSF protein concentration and CSF cell count.

DISCUSSION

TBM remains a major global health problem and even in developed countries there is a resurgence of tuberculous infection due to growing number of people infected with hu-man immunodeficiency virus (HIV). Early confirmatory diagnosis of TBM is difficult to establish because of its pleomorphic clinical presentation.[13-15] The commonly used laboratory method for the definitive diagnosis of TBM is to demonstrate the presence of tu-bercle bacilli either by smear or culture. Direct smear methods are often negative in CSF samples and culture of MTB takes 4-6 weeks and in most cases negative.[16] Newer methods such as PCR and comparable systems are incompletely assessed and not affordable. The increased ADA activity as a marker of cell mediated immunity is 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 other CNS infections.[17] Other researchers have also observed the usefulness of CSF ADA activity in the diagnosis of TBM

In the present study, CSF ADA level 10 U/L for the diagnosis of TBM had sensitivity of 90.62% and specificity of 95.65%. The result of the present study showed that mean CSF ADA level in TBM patients was 12.32U/L which was significantly raised ($p < 0.001$) as compared to bacterial meningitis, aseptic meningitis a finding similar to that of various other studies. The mean CSF ADA levels in TBM cases of pediatric age group have been reported to be ranging between 11.6 to 13.6 U/L. In previous studies a relatively higher mean CSF ADA values of 15.7 - 21.3 U/L have been observed in adult patients. These results showed that ADA secretion by T-lymphocytes in response to mycobacterial antigen vary and lower activity is observed in CSF of pediatric TBM patients. It may be due to difference in the immunological reactivity to tubercular antigen in children as com-pared to adults.[18-23]

Mishra et al demonstrated that mean CSF ADA activity in tuberculous meningitis was 9.4U/L which was significantly elevated as compared to partially treated bacterial meningitis. Malan et al also demonstrated the same significant difference level between the two groups. Baheti et al found that CSF ADA level of 6.5IU/L may differentiate tuberculous from non-tuberculous etiology.

CONCLUSION

Tuberculous meningitis is a major global health problem. The diagnosis of tuberculous meningitis is complicated as it causes various clinical manifestations which overlap with other non-tuberculous etiologies. ADA activity in CSF is rapid and affordable adjunct in differentiating tuberculous from non-tuberculous meningitis. Other researchers have also observed the usefulness of CSF ADA activity in the diagnosis of tuberculous meningitis.

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