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DIAGNOSTIC VALUE OF ADENOSINE DEAMINASE (ADA) ACTIVITY IN EXTRA PULMONARY TUBERCULOSIS

Microbiology

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ABSTRACT

Introduction: Tuberculosis is one of the commonest chronic infectious diseases, which is highly endemic in India. It usually affects lungs but cases of extra pulmonary tuberculosis are not rare. In a large percentage of cases, involvement of pleura, peritoneum, meninges and synovial membranes is also common. Pulmonary tuberculosis can be confirmed by sputum examination and diagnosed easily, but diagnosing extra pulmonary TB becomes frequently difficult since the specificity and sensitivity of non – invasive methods is low. Adenosine deaminase (ADA) has been proposed to be useful surrogate marker for tuberculosis in pleural, pericardial, peritoneal fluids and cerebrospinal fluid (CSF).

Objective: The aim of the study is to assess the diagnostic value of ADA in extra pulmonary tuberculosis.

Materials and Methods: The study was carried out during the period of October, 2015 to June, 2016 on 100 patients suffering from serosal effusion (50 pleural, 30 peritoneal and 20 samples of CSF). Detailed clinical history, physical examination and routine and relevant investigation of all patients including ADA estimation by Galanti and Guisti method was done.

Results: Out of 100 patients of serosal effusion, 43 were of tubercular and 57 of non-tubercular etiology. ADA level in tuberculous pleural effusion ranged from 43.0 -187.9 U/L with a mean level of 102.0 U/L. ADA level in tubercular peritoneal effusion ranged from 41.5 – 246 U/L with a mean level of 105.8 U/L. ADA level in CSF from tuberculosis meningitis patients ranged from 11.5 – 77.0 U/L with a mean level of 29.6 U/L. Overall serosal fluid ADA estimation offers high degree of sensitivity and specificity of about 98% and 95% respectively.

Conclusion: The method of ADA estimation is easy, simple and doesn't require expensive equipment. The present study shows that a simple, inexpensive, highly sensitive and specific test like ADA estimation should be employed as a marker to diagnose extra pulmonary tuberculosis.

KEYWORDS

Adenosine deaminase, extra pulmonary tuberculosis

INTRODUCTION

Tuberculosis (TB) is one of the commonest chronic infectious diseases, which is highly endemic in India and five lakh patients die every year [1]. It is the second leading infectious cause of death after Human Immunodeficiency Virus (HIV) infection [2]. It is a chronic specific bacterial infection caused by the bacteria Mycobacterium tuberculosis [3]. It usually affects lungs, but cases of extra-pulmonary tuberculosis are not rare. Delay in diagnosis and in initiating treatment results in poor prognosis and sequel in up to 25% of cases [4]. In large number of cases, involvement of pleura, peritoneum, meninges and synovial membranes is also common. Pulmonary tuberculosis can be confirmed by sputum examination and diagnosed easily, but diagnosing extra-pulmonary TB becomes usually difficult since the sensitivity and specificity of non-invasive methods is very low [5].

Adenosine deaminase (ADA) has been proposed to be useful surrogate marker for tuberculosis in pleural, pericardial and peritoneal fluids. Studies have confirmed high sensitivity and specificity of adenosine deaminase for early diagnosis of extra-pulmonary tuberculosis.

Adenosine deaminase is an enzyme in the purine salvage pathway that catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine 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 [6]. 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 adenosine deaminase. Likewise, a deficiency of adenosine deaminase is associated with severe defects in the cell-mediated and humoral arms of the immune system, predisposing the patient to opportunistic infections. Tuberculous effusion is the result of a cell-mediated immune response to the presence of Mycobacterium tuberculi and is characterized by the accumulation of activated T-lymphocytes and macrophages. Since adenosine deaminase is increased in TB effusions and is an easy little-invasive investigation, it is frequently considered as a diagnostic aid in such cases with a sensitivity of 90-100% and specificity 89-100% [7-8].

AIM AND OBJECTIVE

The aim of the study is to assess the diagnostic value of ADA estimation in extrapulmonary tuberculosis.

MATERIAL AND METHODS

The study was conducted during the period of October 2015 to June 2016 in the department of Microbiology at Indira Gandhi Institute of Medical Sciences (IGIMS), Patna after getting approval from the Institutional Ethics Committee. In this study 100 patients suffering from serosal effusion (50 pleural, 30 peritoneal) and 20 patients suffering from meningitis were included. Detailed clinical history, physical examination, investigations, for example, Hb, T/DLC, ESR,

GBP, CBC, SGOT, SGPT, PPD test and X-ray/ultrasound were done in all the cases. AFB in the sputum/fluid, AFB culture, ECG, cytology and biopsy with its histopathological examination were done in selective cases.

Presence of first or more than one of the following criteria were adopted to label a case as tuberculous: (1) Bacteriological confirmation of presence of Mycobacterium tuberculosis (direct smear or culture or histological finding); (2) Histopathology finding of caseous granulomas; (3) Radiological findings consistent with TB; (4) Clinical presentation consistent with TB with exclusion of other clinical considerations; (5) Definite clinical and radiological improvement in two months on administration of exclusive anti-tuberculosis treatment; (6) History of contact with current disease and positive reaction (more than 10 mm induration) to 5 tuberculin unit (TU) purified protein derivative (PPD).

ADA estimation was done by using Microexpress ADA – MTB reagent according to manufacturer's instruction.

REFERENCE VALUES

Serum, plasma, pleural, pericardial and ascetic fluid	Normal Suspect Positive	< 30 U/L 30 U/L to 40 U/L >40 U/L
CSF	Normal Positive	<10 U/L >10 U/L

RESULTS

Out of 100 patients of serosal effusion, 43 were of tubercular and 57 were of non – tubercular etiology. ADA level in tuberculous pleural effusion ranged from 43.0 – 187.9 U/L with a mean level of 102.0 U/L. ADA level in tubercular peritoneal effusion ranged from 41.5 – 246 U/L with a mean level of 105.8 U/L. ADA level in CSF ranged from 11.5 – 77.0 U/L with a mean level of 29.6 U/L. overall serosal fluid ADA estimation offers high degree of sensitivity and specificity of 98% and 95% respectively.

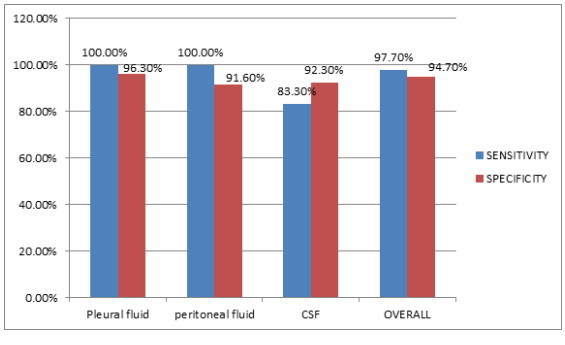
TABLE 1: DISTRIBUTION OF SAMPLES

Sample	Total no.	Tubercular	Non - tubercular
Pleural fluid	55	23	32
Peritoneal fluid	26	14	12
CSF	19	6	13
Total	100	43	57

TABLE 2 : ADA LEVEL IN VARIOUS SAMPLES

Sample		Mean (U/L)	Range (U/L)
Pleural fluid	Tubercular	102.0	43.0-187.9
	Non tubercular	13.97	1.7-38.0
Peritoneal fluid	Tubercular	105.8	41.5-246
	Non tubercular	10.6	0.3-37.9
CSF	Tubercular	29.6	11.5-77.0
	Non tubercular	3.8	0.02-9.6

Chart 1: Sensitivity and Specificity of ADA Detection



DISCUSSION

Tuberculosis is entirely regulated by cell mediated immune response (CMI) of the host. When bacillary antigens are present at low levels the CMI response causes macrophages to accumulate, get activated then destroy the bacilli. When the bacillary antigen are present at high levels the CMI response causes necrosis of tissue. Immune response against Mycobacterium Tuberculosis involves both macrophages and lymphocytes, dead organism, are broken down relatively within the granuloma, releasing large quantities of glyco-lipid and polysaccharides antigen into the draining lymph nodes leads to predominately humoral immune response. But viable mycobacterium release small quantities of glycoproteins, antigen which induces a delayed hyper sensitivity and cell mediated immune response. A marker of such delayed hypersensitivity is the enzyme, Adenosine deaminase. With its concentration being higher in T- Lymphocytes, key cell of cellular immunity, ADA assay has been considered as a sensitive marker of tubercular effusion which can be routinely used for the diagnosis of tubercular effusion precluding other test which are time consuming as well are very expensive. These characteristics makes ADA assay a very feasible test even in a small size laboratories.

Almost all research workers have shown sensitivity and specificity of 90% to 100% for the value of ADA in pleural fluid using different cut off levels. Gupta, D.K[15] studied 53 cases of pleural effusion out of which 36 were of tuberculous etiology. The mean ADA level in tuberculous was 50.75 U/L while in malignant and parapneumonic effusion it was 14.47 U/L and 28.65 U/L respectively. The sensitivity and specificity for diagnosing tuberculosis were 100% and 94.1 % respectively. In the present study, ADA level in tuberculous pleural effusion ranged from 43.0 – 187.9 U/L with a mean level of 102.0 U/L which is higher as compared to non tubercular cases. The sensitivity and specificity were 100% and 96.30% respectively which is similar to other previous studies.

Burgess L.J.[16] showed ADA activity in tuberculous effusion was higher than in any other diagnostic group. At a level of 50U/L the sensitivity and specificity for the identification of tuberculosis was 90% and 89% respectively. Twenty four ascites cases were studied by Gupta V.K.[17] of whom 7 were due to tubercular etiology with an ADA level of >30 U/L and sensitivity and specificity of 100% and 94.1% respectively. The sensitivity and specificity for tubercular ascites on the basis of ADA level were 100% and 97% respectively as per the study of Bhargawa D.K[18]. In the present study also, The sensitivity and specificity for tubercular ascites on the basis of ADA level were 100% and 91.6% respectively.

ADA level in CSF ranged from 11.5 to 77.0 U/L with a mean of 29.6 U/L in tuberculous meningitis. In non tubercular meningitis , ADA levels ranged from 0.02 to 9.6 U/L with a mean of 3.8 U/L which is lower in comparison to that in tubercular meningitis. Rana et al (2004) found that mean ADA levels in CSF were highest in TB meningitis patients as compared to pyogenic meningitis and aseptic meningitis[19]. Ribera et al (1987) has also demonstrated similar findings in their study of adult TB meningitis patients[20]. Baheti et al (2001) found that CSF - ADA level 6.5 IU/L as a cutoff value exhibited a sensitivity of 95.83%, specificity of 92.85% for the diagnosis of tuberculous meningitis[21].

CONCLUSION

The method of ADA estimation is easy, simple and doesn't require expensive equipment or elaborate laboratory arrangement except a simple colorimeter. It takes only 2 hours and it is also cheap.

The present study shows that a simple, inexpensive, highly sensitive and specific test like ADA estimation should be employed routinely to differentiate between tubercular and non-tubercular etiology in patients of pleural, and peritoneal effusion and in meningitis patients.

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