Original Research Paper Medicine

Role of Adenosine deaminase in evaluating tubercular and non-tubercular pleural effusions

Dr Rajat Arora (DNB Family Medicine) Resident IGGGHPGI Puducherry.

Dr Swati Duggal (MD Microbiology) Resident Dr SN Medical College, Jodhpur.

Dr MJ Stanley Ambroise MD Specialist Grade I General Medicine IGGGHPGI Puducherry.

ABSTRACT

Introduction: Tuberculosis is commonest disease affecting all age-groups and socioeconomic classes, and 7th leading cause of death. Inspite of extensive efforts, definite diagnosis of TB remains challenging. However, rapid, non-invasive and cost-effective method of Adenosine Deaminase(ADA) estimation in clinical samples seems to be promising for its early detection. Aims and Objectives: Comparison of mean serum and pleural fluid ADA levels in tuberculous and non-tuberculous pleural effusion. **Materials and Methods:** A prospective study was conducted in Puducherry in which 80 patients were enrolled for 15-months, 40 each of tuberculous and non-tuberculous pleural effusion. **Results:** In serum, at > 17.9 U/L ,sensitivity and specificity were 93.3 and 51.0% respectively. Positive(PPV) and negative predictive values(NPV) were 62.5% and 88% respectively. In pleural fluid, at > 40 U/ Lit, sensitivity and specificity was 80.55% and 62.32% with 52.73% PPV 80%NPV. Conclusion: Serum and pleural fluid ADA was significantly higher in tuberculous pleural effusion patients.

KEYWORDS : ADA,Pleural effusion,TB

INTRODUCTION:

TB is one of the oldest and commonest infectious diseases also known as "master of death" or "Captain of death".1 It is still a global health issue and is seventh leading cause of death worldwide.2 The severity of the disease can be judged by the fact that it affects all ages, irrespective of the sex ans holds particular significance in a developing country like India. TB is chronic granulomatous bacterial infection, caused mainly by Mycobacterium tuberculosis. TB is categorised as pulmonary and extra-pulmonary tuberculosis. The main symptoms are chronic cough, low grade fever (evening rise of temperature), haemoptysis, chest pain, dyspnoea, loss of weight, unresolved pneumonia.3 Its complications being massive haemoptysis, cor pulmonale, fibrosis/emphysema, calcification, obstructive airway disease, bronchiectasis, bronchopleural fistula.4 Tuberculosis still remains a diagnostic challenge. It can be diagnosed by Mantoux test, acid fast bacilli(AFB) staining, sputum culture, X-ray chest and polymerase chain reaction (PCR). All of these diagnostic methods have a low yield. Unless and until a proper diagnosis is made, TB will remain a major health concern. Direct analysis of pleural fluid for detection of AFB by the Ziehl-Neelsen stain (ZN) is positive in <5% cases and the culture on Lowenstein-Jensen (LJ) medium gives a positivity rate of 40 % in >4 weeks.5 Thus, there is a need for single test, that is adequately sensitive and specific, at the same time, inexpensive and easy to perform.6

Adenosine deaminase (ADA) is the enzyme involved in breakdown of adenosine to uric acid.6 Physiologic role of ADA is especially important in lymphoid tissue. It is distributed ramdomly in human body but highest in lymphocytes.7 Estimation of serum ADA activity is a simple, rapid, non-invasive and relatively less expensive method,8,9 It helps in early diagnosis and treatment of the patient and prevents the spread of disease in the community.10

Although the sensitivity and specificity of ADA estimation and its cut off value in distinguishing tuberculous effusion from non tuberculous effusion is different in different studies.Therefore, this study was planned to determine the exact role of ADA in TB patients with and without pleural effusion.

AIMS AND OBJECTIVES

1. To determine mean values of serum ADA in patients of TB with pleural effusion and in non-tuberculosis pleural effusion.
2. To compare value of ADA in pleural fluid in patients of TB with pleural effusion and non TB pleural effusion.

MATERIALS AND METHODS:

This was a 15-month (Jan 2015 to March 2016) prospective study conducted in Indira Gandhi Government General Hospital & Post Graduate Institute(IGGGH & PGI), Puducherry, India in which 80 patients in 19 - 83 years were included. Voluntary participation and informed consent was taken from patients before collecting the samples.

Inclusion criteria:

Microbiologically and radiologically confirmed cases of TB with pleural effusion and nontubercular effusion (unilateral or bilateral), of either sex and age >18 years.

Exclusion criteria:

- Patients who have taken antitubercular treatment before developing pleural effusion.
- Pregnant and lactating women, patients <18 years.
- Participants on Drugs which affect ADA values like interferon alpha, deoxycoformycin, ribavirin and viramidine.

Principle:

Adenosine deaminase hydrolyses adenosine to ammonia and inosine. The ammonia formed further reacts with 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.1
Stastical analysis: One way ANOVA test.

RESULTS:

80 consecutive patients of pleural effusion who came for medical attention between Jan 2015 to March 2016 in IGGGH & PGI hospital were studied. Forty patients with effusion secondary to tuberculosis (group I). Rest (group II) of the cases were diagnosed to have malignancy (n=21), nephrotic syndrome (n=11), cirrhosis (n=6) and congestive cardiac failure (n=2).

Table 1: Categorisation of patients in different study group (N = 80).

Study group	No. of patients	Nature of group
I	40	TB with pleural effusion
II	40	Non-tuberculous pleural effusion

Mean age of patients having tuberculosis was 34 years (Age Range: 19-83 years) with 31 males and 9 females and non-tuberculous pleural effusion was 39 years (Age range: 23-76 years) with 29 males and 11 females.

Table 2: Comparision of mean values of ADA (U/L) in serum:

Groups	Range (U/L)	Mean ADA +/- SD	P value
I	17.7-54.1	31.99 +/- 8.85	<0.0001
II	18.8-29.8	14.84 +/- 2.43	<0.0001

(P value <0.05 was considered significant)

Table 3: Comparision of mean values of ADA (U/L) in pleural fluid:

Groups	Range (U/L)	Mean ADA +/- SD	P value
I	42.6-102.4	81.04 ± 19.78	<0.0001
II	19.3-49.2	27.72 + 7.80	<0.0001

The ROC curve was done to determine cut off value for both serum and pleural fluid ADA to predict the presence or absence of tuberculosis. In serum cut off value of ADA was 17.9 U/L and sensitivity of this marker was 93.3, specificity was 51.0%. Positive predictive value was 62.5% and negative predictive value was 88%. In pleural fluid, at > 40 U/ Lit, the sensitivity and specificity of the test was 80.55% and 62.32%, with a positive predictive value 52.73% and negative predictive value 80%. This was the best cut off point and confirmed by plotting ROC curve.

DISCUSSION:

Significantly increased ADA activity (p<0.001) in the serum of tubercular pleural effusion patients compared to non-TB pleural effusion is due to activation of cell mediated immunity. In tuberculosis there are increased numbers of T-lymphocytes and macrophages in pleural fluid which may be associated with highly elevated ADA activity in such patients. In pathological conditions, the clearance capacity of lungs is decreased leading to increased numbers of cells in pleural fluid and the recirculation of activated T-cells may cause a high serum ADA activity in patients with pulmonary disease.11

In the present study, there was statistically significant increase (p<0.001) in mean serum and pleural fluid ADA levels in patients of TB with effusion as compared to non-TB pleural effusion patients which is in accordance with different studies.

Sonone Kanchan K. et al(2015)12 did their study on 132 subjects and concluded that serum ADA levels in pulmonary tuberculosis (55.09 + 11.02) patients and pulmonary tuberculosis with pleural effusion (44.01 + 7.82) were significantly higher (p <0.001) when compared with healthy controls (18.11 + 6.13). similarly, Pleural fluid ADA levels were significantly higher (p <0.0001) in pulmonary tuberculosis with pleural effusion (82.61+ 12.03) than in non tuberculosis pleural effusion (27.72 +7.80).

Bharat Kumar Gupta et al (2010)13 did similar study in 330 patients with pleural, ascitic, meningeal and synovial effusion (72 with pleural effusion) and found that pleural fluid ADA levels were significantly higher in TB pleural fluid as compared with non TB pleural fluid.

Y.C.Gary Lee et al (2001)14 studied 106 cases of lymphocytic pleural effusion of different etiologies and concluded that ADA levels in TB pleural fluid exceeds than that in other non tuberculosis lymphocytic pleural fluid.

The pleural fluid ADA values reported by other Indian authors are Sinha et al15 (1985) 76.8 ± 23.8 U/Lit, Baldev Raj et al16 (1985) 99.56 ± 9.78 U/Lit, Gilhotra R. et al17 (1989) 82.9 ± 30.32 U/Lit, Saoji et al18 (1987) 73.6 ± 28.1 U/Lit respectively.

Way back in 2001,S K Sharma et al6 did their study on 75 patients and concluded that if 100 IU/L is set as the as the cut-off for ADA, pleural biopsy as a diagnostic tool can be avoided in as much as 40 % of patients. They also stated that ADA estimation is adequately sensitive, specific, inexpensive and easy to perform for diagnosis of TB. Moreys C. K. et al (2004)4 also concluded that pleural fluid ADA determination is a sensitive and specific method for diagnosis of pleural TB and its use can avoid pleural biopsy at least in initial workup of pleural effusion of patients.

CONCLUSION:

Serum and pleural fluid ADA was significantly higher in patients of TB with pleural effusion as compared to non TB pleural effusion. Also, Pleural fluid ADA was higher than serum ADA levels. Thus serum ADA and pleural fluid ADA plays a very important role in distinguishing tubercular from non tubercular causes of pleural effusion. Also, ADA estimation, is relatively inexpensive, rapid and reliable investigation, specially in resources restricted areas.

REFERENCES:

[1] Mathur PC, Tiwari KK, Trikha S and Tiwari D: Diagnostic utility of Adenosine deaminase (ADA) activity in Tubercular serositis. Indian journal of Tuberculosis 2006; 53:92-95.
[2] Tuberculosis: A leading killer disease – Health and Fitness – Life and Style; article show. 2009; Dec 4.
[3] Kumar P, Clark M. Infectious diseases. In: Kumar and Clark Clinical Medicine. 6th edition. Elsevier, Saunders. 2005: 86-91.
[4] Kaisemann MC, Kritski AL, Pereira M.F.C, Trajman A. Pleural fluid adenosine deaminase detection for the diagnosis of pleural tuberculosis J Bras Pneumol 2004; 30(6).
[5] Light RW. Useful tests on the pleural fluid in the management of patients with pleural effusions. Curr Opin Pulm Med 1999; 5: 245-52.
[6] Sharma SK, Suresh V, Mohan A, et al A prospective study of sensitivity and specificity of adenosine deaminase estimation in the diagnosis of tuberculosis pleural effusion. Indian J Chest Dis Allied Sci 2001; 43,149-155.
[7] Gajdos A. Familial immune deficit and genetic deficiency of ADA of nucleotide phosphorylase. Nour press Medicine 1978 Mar 18; 7(11):929-34.
[8] Gupta BK, Bharatb V, Bandyopadhyay D. Role of Adenosine Deaminase Estimation in Differentiation of Tuberculous and Non-tuberculous Exudative Pleural Effusions. J Clin Med Res 2010; 2(2):79-84.
[9] Chander A, Shrestha C.D. Diagnostic value of serum adenosine deaminase levels in sputum smear negative pulmonary tuberculosis patients in Nepalese population. Asian Pacific Journal of Tropical Biomedicine (2012) S1896-S1899.
[10] Devkota KC, Shyam BK, Sherpa K, Ghimire P, Sherpa MT, Shrestha R and Gautam S. Significance of adenosine deaminase in diagnosing tuberculous pleural effusion. Nepal Med Coll J 2012; 14(2): 149-152.
[11]. Fonts BM, Pego A, Lima MA, Gaspar EV, Robalo CA. Serum and pleural Adenosine deaminase: correlation with lymphocyte populations. Chest 1990; 97: 605-610.
[12] Sonone et al. Study of Adenosine Deaminase Levels in Patients of Pulmonary Tuberculosis with and Without Pleural Effusion. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)2014;13(1):30-37
[13] Gupta BK, Bharatb V, Bandyopadhyay D. Sensitivity, Specificity, Negative and Positive Predictive Values of Adenosine Deaminase in Patients of Tubercular and Non-Tubercular Serosal Effusion in India. J Clin Med Res 2010; 2(3):121-126.
[14] Lee YCG, Rogers JT, Rodriguez RM, Miller KD and Light RW. Adenosine Deaminase Levels in Nontuberculous Lymphocytic Pleural Effusions. Chest 2001; 120:356–361.
[15]. Sinha, P.K. et al: Diagnosing tuberculous pleural effusion, comparativo sensitivity of mycobacterial culture, histopathology and ADA activity, JAPI; 1985, 30 (10), 644.
[16]. Baldev Raj, Chopra, R.K. et al : Adenosine deaminase activity in pleural fluids : a diagnostic aid in TB pleural effusion. Ind. J. Chest Dis., Allied Sci.; 1985, 27 (2), 76.
[17]. Gilhotra, R., Seagal, S. and Jindal, S.K.: Pleural biopsy and ADA enzyme activity in effusions of different etiologies, Lung India (1989) VII, No. 3 (p-122-124).
[18] Saoji, et al. ADA in pleural fluid- an aid to diagnosis tubercular pleural effusion. Tubercle; 1988,35,92