Galore International Journal of Health Sciences and Research
Vol.5; Issue: 2; April-June 2020
Website: www.gijhsr.com
Original Research Article *P-ISSN: 2456-9321*

Study of Pleural Fluid Adenosine Deaminase Levels in Subjects with Tubercular and Non-Tubercular Pleural Effusion

Dharampal, Arun Sharma

Assistant Professor, Dept. of General Medicine, World College of Medical Sciences and Research, Jhajjar, Haryana

Corresponding Author: Arun Sharma

ABSTRACT

Introduction: Tuberculosis is the communicable infectious disease usually caused by Mycobacterium Tuberculosis Bacteria (MTB). Tuberculosis generally affects lungs, but can also affect other parts of the body. As of 2018 one-quarter of the world's population is thought to be infected with TB. Tuberculous pleuritis occurs due to delayed hypersensitivity reaction with paucity of bacillary load in the fluid. Lymphocytic exudate alone is not able to confirm the diagnosis of tuberculosis. ADA has been found to be useful parameter to conclude the tubercular etiology.

Material and Methods: 80 subjects suspected of tuberculous pleuritis were subjected to cytological and ADA evaluation. Tuberculosis was confirmed by ZN stain, AFB culture and other relevant investigations.

Result: Out of the 80 subjects, 59 (73.7%) were males and 21 (26.5%) were females. The mean age and SD in males is 46±16.18 and females is 45.9±16.4 respectively. ADA levels were measured in all the subjects, out of which 46 were found to have ADA <40 IU/L and 34 were having ADA >40 IU/L. Cytological examination revealed lymphocytic exudates in 55 (68.5%) subjects and 25 (31.25%) had <50% lymphocytic exudates. Pleural fluid protein was elevated (>3gm/dL) was seen in 31(38.75%) subjects were positive for AFB and 49 (61.25%) had pleural fluid protein <3gm/dL. Total numbers of tubercular cases were 31 (38.75% cases). Out of 31 tubercular subjects, 27 (87%) had elevated ADA >40 IU/L and 4 (12.9%) had ADA levels <40 IU/L. Diagnostic validity of ADA test between tubercular and non-tubercular pleuritis revealed Sensitivity of 87%, Specificity of 85.7%, PPV of 79.4% and NPV of 91.3%.

Conclusion: ADA estimation with cytology increases the sensitivity, specificity and predictive value of ADA in the diagnosis of tuberculous pleuritis. Therefore, ADA should be included as routine investigation for pleural fluid analysis.

Keywords: ADA, pleural fluid, predictive value, Sensitivity, specificity

INTRODUCTION

Tuberculosis is the communicable infectious disease usually caused by Mycobacterium Tuberculosis Bacteria (MTB). Tuberculosis generally affects lungs, but can also affect other parts of the body. As of 2018 one-quarter of the world's population is thought to be infected with TB. New infections occur in about 1% of the population each year. In 2017, there were about more than 10 million cases of active TB which has caused 1.6 million deaths. More than 95% of the deaths occurred in developing countries and more than 50% in India, China, Indonesia, Pakistan and Phillipines.[1]

Pleural tuberculosis is common manifestation of extra pulmonary TB, with or without pulmonary TB. Tuberculous pleurisy is present in around 4% of all TB cases. Tuberculous Pleural effusion is diagnosed by demonstration of tubercular bacilli in pleural fluid or granuloma in pleural biopsy specimen. Since pleural biopsy is more difficult than pleural

aspiration, various parameters have been developed and evaluated as an alternative to pleural biopsy. [2,3,4]

Adenosine Deaminase (ADA), is an enzyme which catalyses the conversion of adenosine to inosine and plays an important role in the differentiation of lymphoid cells. Pleural Fluid ADA has thus become an important diagnostic tool in the evaluation of exudative pleural effusions because it is inexpensive, rapid and has high sensitivity and specificity of 100% and 95% respectively for diagnosis of tubercular pleural effusion (TPE).[5] The combination of ADA and pleural fluid lymphocyte proportion has come to be recognized as an excellent approach for increasing the specificity of ADA test.[6]Although pleural fluid ADA is not a perfect discriminator, its level is considerably elevated in patients with TPE. High ADA levels can sometimes be observed in pleural fluid from patients of empyema, malignancies, collagen vascular disease, chylothorax and post coronary artery bypass graft (CABG). Therefore, presence of raised pleural fluid ADA is considered a useful marker for diagnosis of TPE, especially in patients with exudative and lymphocytic pleural effusion in high TB burden settings.

These patients can empirically be started on anti-tuberculous therapy if no other investigation can provide a definite diagnosis. Similarly, low pleural fluid ADA may be useful in excluding TPE, especially in a patient with low pre-test probability. The pleural fluid of tubercular pleuritis is predominantly lymphocytic but in acute tubercular pleuritis there may be increase in neutrophils.[7,8,9] Hence, we have taken up this study to estimate the levels of ADA in subjects with tubercular and non-tubercular pleural effusion admitted to our hospital.

OBJECTIVES OF THE STUDY: The objectives of our study include,

1. To estimate the ADA levels in subjects with both tubercular and non-tubercular effusion.
2. To find out the specificity, sensitivity, positive predictive value and negative predictive value of ADA in tubercular pleural effusion.

MATERIALS AND METHODS

Source of Data: A Hospital Based Prospective Cross-Sectional Study was conducted on "study levels of ADA in subjects with tubercular and non-tubercular pleural effusion admitted to our hospital was conducted at World College of Medical Sciences and Research, Jhajjar, Haryana from Jan to June 2019. A total of 80 suspected cases of tubercular pleural effusion fluid were sent for diagnostic evaluation.

Laboratory Analysis: Biochemical analysis for Protein and Glucose were performed on Automated Biochemistry Analyser and ADA was estimated by ADA-MTB kit method.[10]Cytological examination (cell count, cell type, malignant cells) and ADA Microbiological demonstration of AFB by ZN stain and AFB culture was done by conventional LJ method. After all relevant investigation, lymphocytic exudates were segregated with >50 % lymphocytic proportion of all nucleated cells. ADA level cut-off >40IU/ L were considered as tuberculous exudates which were confirmed by AFB stain and AFB culture subsequently. ADA level cut off value <40IU/L were studied for cytological examination for malignant cells and relevant investigation to confirm non-tuberculous lesion.

Statistical Analysis: Data were expressed as mean±SD. The Student *t* test was used for the comparison. The results of the diagnostic tests were expressed as sensitivity, specificity, predictive values (positive and negative) and accuracy, with 95% confidence intervals (95% CI).

RESULTS

A total of 80 subjects suspected of tubercular pleural effusion were included in the study. Out of the 80 subjects, 59 (73.7%) were males and 21 (26.5%) were females. The mean age and SD in males is

46±16.18 and females is 45.9±16.4 respectively (table 1). ADA levels were measured in all the subjects, out of which 46 were found to have ADA <40 IU/L and 34 were having ADA >40 IU/L (table 2). Cytological examination revealed lymphocytic exudates in 55 (68.5%) subjects and 25 (31.25%) had <50% lymphocytic exudates (table 3).Pleural fluid protein was elevated (>3gm/dL) was seen in 31(38.75%) subjects were positive for AFB and 49 (61.25%) had pleural fluid protein <3gm/dL (table 4). Total numbers of tubercular cases were 31 (38.75% cases). Out of 31 tubercular subjects, 27 (87%) had elevated ADA >40 IU/L and 4 (12.9%) had ADA levels <40 IU/L (table 5 & 6).Diagnostic validity of ADA test between tubercular and non-tubercular pleuritis revealed Sensitivity of 87%, Specificity of 85.7%, PPV of 79.4% and NPV of 91.3% (table 7).

Table 1: Shows Age and Gender wise distribution of the subjects with Pleural Effusion

Age Groups (years)	**Number of Subjects**	**Males**	**Females**	**Percentage**
11-20	2	1	1	2.5
21-30	16	12	4	20
31-40	18	14	4	22.5
41-50	20	17	3	25
51-60	7	5	2	8.75
61-70	16	10	6	20
71-80	1	-	1	1.25
Total	80	59	21	
Percentage		73.7%	26.5%	

Table 2: Distribution of Subjects Depending on ADA levels <40 and >40 IU/L

ADA <40 IU/L	**46**
ADA >40 IU/L	**34**

Table 3: Distribution of ADA and Lymphocyte Exudate

	ADA <40 IU/L	**ADA >40 IU/L**
>50% Lymphocytic Exudate	24	31
<50% Lymphocytic Exudate	22	3
Total	46	34

Table 4: Distribution of Subjects Depending on Pleural Fluid Protein levels <3gm/dL and >3gm/dL

	ADA <40 IU/L	**ADA >40 IU/L**
<3gm/dL (n=27)	27	-
>3gm/dL (n=53)	22	31
Total	49	31

Table 5: Distribution of Subjects Depending on AFB culture and ADA levels

	ADA <40 IU/L	**ADA >40 IU/L**
AFB Culture Positive	4	27
AFB Culture Negative	45	4
Total	49	31

Table 6: ADA Status in Tubercular and Non-Tubercular Pleuritis

	Non-Tubercular Pleuritis	**Tubercular Pleuritis**	**Total**
ADA <40 IU/L	42	4	46
ADA >40 IU/L	7	27	34
Total	49	31	80

Table 7: Validity of ADA test for Tubercular and Non-Tubercular Pleuritis

Sensitivity	87%
Specificity	85.7%
Positive Predictive Value	79.4%
Negative Predictive Value	91.3%

DISCUSSION

Pleural effusion is a common clinical entity: approximately 4% of all attendances at chest clinics. The initial step in diagnosis is to distinguish between transudates and exudates. [11,12,13,14] This is indicative of the underlying pathophysiological process involved. Such a distinction allows appropriate investigations to be instigated, enabling better patient management. The causes for exudative pleural effusion include tuberculosis, lung cancer, breast cancer, pneumonia, systemic lupus erythematosus, Meigs' syndrome, mesothelioma, pancreatic pseudocyst etc. The diagnosis of tubercular pleural effusion is challenge in clinical practice. The commonest cause of pleural effusion has been found to be tuberculosis (60.2%) followed by malignancy (29.1%) and pneumonitis (7.7%).[15-18] Although lymphocytic predominance is usually seen in tubercular pleural effusion but needs to be differentiated from malignancies. Hence, there is need to differentiate among various causes of pleural effusion. It has been observed that determination of ADA is more sensitive than histopathological examination of pleural tissue. The combination of

effusion and sputum culture may give a good diagnostic clue but tuberculous pleurisy is a hypersensitivity reaction, therefore an alternate approach to diagnose tubercular pleurisy is ADA determination. The McNemar test demonstrated that from a statistical view point ADA determination was more sensitive than pleural histopathological examination. Cut off value of ADA varies in various studies from 30 IU/L to 40 IU/L. We have used cut off 40 IU/L to increase specificity.[19,20] In our study, we found the sensitivity of 87% and specificity of 85.7%. This was in accordance with the studies reported in the past. [21,22] We also found high negative predictive value of 91.3% and positive predictive value of 79.4%. Therefore, the measurement of pleural fluid ADA is an excellent biomarker to rule out tubercular aetiology of lymphocytic exudates.

CONCLUSION

ADA estimation with cytology increases the sensitivity and specificity and predictive value for the diagnosis of tuberculosis. A cut off 40 IU/L is considered to be adequate to exclude tuberculosis. All cases of lymphocytic pleural effusion should be screened for ADA to exclude tuberculosis.

REFERENCES

1. 'Tuberculosis Fact Sheet N 104" World Health Organization (WHO). October 2015.
2. Sharma SK, Mohan A. Extrapulmonary tuberculosis. Indian J Med Res. 2004; 120:316-53.
3. Light RW. Tuberculous pleural effusions. In: Light RW, editor. Pleural Diseases. 5th Edition. Baltimore: Lippincott, Williams and Wilkins. 2001:182-195.
4. Krenke R, Korczyński P Use of pleural fluid levels of adenosine deaminase and interferon gamma in the diagnosis of tuberculous pleuritis.Curr Opin Pulm Med. 2010;16:367-75.
5. Valdes L, San Jose E, Alvarez D, et al: Diagnosis of tuberculous pleurisy using biologic parameters adenosine deaminase, lysozyme and interferon gamma. Chest. 1993, 103:458-465
6. Burgess LJ, Maritz FJ, Le Roux I, Taljaard JJ. Combined use of pleural adenosine deaminase with lymphocyte/ neutrophil ratio. Increased specificity for the diagnosis of tuberculous pleuritis. Chest 109:414-419. Chest. 1996; 109:414-9.
7. Hooper C, Lee YC, Maskell N. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii4–17.
8. Vorster MJ, Allwood BW, Diacon AH, Koegelenberg CF. Tuberculous pleural effusions: advances and controversies. J Thorac Dis. 2015;7(6):981–91. pmid: 26150911
9. Porcel JM. Tuberculous pleural effusion. Lung. 2009;187(5):263–70. pmid: 19672657
10. Jose L, Banales MD et al.1991 Chest 99/2:355 Sahn SA. The pleura. Am Rev Respir Dis 1988;138:184
11. Light RW, MacGregor MI, Luchsinger PC, Ball WC. Pleural effusion. The diagnostic separation of transudates and exudates. Ann Intern Med 1972;77:507
12. Light RW. Pleural effusion. Med Clin North Am 1977;61:1339
13. Romero S, Chandela A, Martin C et al. Evaluation of different criteria for the separation of pleural transudates from exudates. Chest 1993;104:399
14. L. Valdés, D. Alvarez, E. San José, J. R. Juanatey, A. Pose, J. M. Valle, M. Salgueiro, and J. R. Suárez. Value of adenosine deaminase in the diagnosis of tuberculous pleural effusions in young patients in a region of high prevalence of tuberculosis. Thorax. 1995;50:600–603.
15. Bañales JL, Pineda PR, Fitzgerald JM, Rubio H, Selman M, Salazar-LezamaM. Adenosine deaminase in the diagnosis of tuberculous pleural effusions. A report of 218 patients and review of the literature. Chest. 1991;99:355-7.
16. Mostafa MG, Khatun A, Islam K, Zaman AMI. Diagnostic significance of pleural fluid adenosine deaminase activityin tuberculous pleurisy Chest and Heart Bulletin. 1996;10:47- 52.
17. Haque ME, Ahmad MM, Hiron MM. Aetiological diagnosis of pleural effusion. Chest and Heart Journal. 2000;24:1-4.

18. Valdés L, San José E, Alvarez D, Sarandeses A, Pose A, Chomón B. Value of adenosine deaminase in the diagnosis of tuberculosis of pleural effusion in young patients in a region with high prevalence of tuberculosis. Thorax. 1995;50:600–603.
19. Porcel JM, Esquerda A, Bielsa S. Diagnostic performance of adenosine deaminase activity in pleural fluid: a single-center experience with over 2100 consecutive patients. Eur J Intern Med. 2010; 21:419-23.
20. Diacon HA, Van de wal, Wyser C, Smedema JP et al. Diagnostic tools in tuberculous pleurisy: a direct comparative study. EurRespir J. 2003;22:589-591.
21. Chen ML, Yu WC, Lam CW, Au KM, Kong FY, Chan AY. Diagnostic value of pleural fluid Adenosine deaminase activity in tuberculous pleuritis. ClinChimActa. 2004;341:101-7.

How to cite this article: Dharampal, Arun Sharma A. Study of pleural fluid adenosine deaminase levels in subjects with tubercular and non-tubercular pleural effusion. Gal Int J Health Sci Res. 2020; 5(2): 21-25.

******