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Evaluation of Efficacy of Serum Adenosine Deaminase Values for Detection of Pulmonary and Extra Pulmonary Tuberculosis

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ABSTRACT

Background

Tuberculosis is one of the leading cause of morbidity and mortality worldwide and in Nepal. Despite advances in its diagnosis, majority of the cases still go undetected. These account for sputum smear negative and extra pulmonary cases where demonstration of the microorganism is challenging. ADA an enzyme found in all mammalian species is found raised in various effusion body fluids of organs affected by the disease. Time tested studies have also shown that serum values of ADA are elevated in patients affected with the disease thus can aid as supportive evidence in doubtful cases.

Methods

An Analytical cross sectional Hospital Based study involving 110 with 75 cases and 35 healthy participants was conducted in College of Medical Sciences for 5 months from January to June 2024. Serum ADA levels were measured in all participants, diseased and healthy and collected data was analyzed for significance.

Results

The mean Serum ADA level in TB patients was found to be 47.01 and that of healthy participants was 14.68. Significant difference in the mean serum ADA level between TB and non TB patients (p-value < 0.001) was found concluding that TB patients have high serum ADA level. Comparisons between mean serum ADA levels in Different types of TB found no significant difference among them with all p- values in each pair being more than 0.5 suggesting that serum ADA levels rise in all forms of TB.

Conclusions

Serum ADA values are raised in all forms of tuberculosis and can serve as a supportive evidence in patients with Smear negative and Extrpulonary TB where microorganisms is difficult to demonstrate. However further validation need to be done by more studies in the future.

Keywords: ADA; tuberculosis; extrapulmonary TB (EPTB).

INTRODUCTION

Tuberculosis (TB) caused by Mycobacterium tuberculosis is a preventable and curable disease. Yet in 2022, more than 10 million people continue to fall ill with TB every year.[1,2] The gold standard for detection of mycobacterium is to prepare a mycobacterium culture which takes 8 weeks. This long lag period predispose patients to be lost to follow up and contributes to fatality if prompt treatment is not initiated based on other findings. Finding acid-fast bacilli in sputum is the quick screening method for pulmonary TB diagnosis but its sensitivity is low and the polymerase chain reaction (PCR) test for TB is expensive and requires skilled personnel and equipment. Therefore, there has been a great search for other biochemical, immunological or microbiological diagnostic methods to diagnosis TB quickly and accurately.[3-5] Adenosine deaminase (ADA), an enzyme of the purine metabolism is present in all mammalian cells and is essential

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for proliferation of lymphoid cells, and helps in the maturation of macrophages. It is an index for cellular immunity[6,7] and studies have proved its raised level in various body fluids effusion as a means TB diagnosis guiding in initiation of ATT.[8-12] Studies done in the past have shown significant relation between the serum levels of ADA and the disease activity thus validating a strong point that serum levels of ADA may be used for detection of pulmonary and extra pulmonary tuberculosis in resource limited settings.

METHODS

We conducted a Analytical cross sectional Hospital Based study in College of Medical Sciences, Department of Internal medicine for 5 months from January to June 2024 A total of 110 patients meeting the inclusion criteria were enrolled for the study after taking written consent. Ethical Clearance was taken from the COMS IRC (Ref. No. (COMSTH-IRC/2023-117). Non probability convenience sampling was used for data collection. A case proforma containing all the variables needed in the study was used to collect the data. Cases of Tuberculosis were labeled as bacteriologically confirmed for sputum smear positive cases or smear negative for radiologically diagnosed or clinically diagnosed. In cases of Tubercular pleural effusion diagnosis was done by Pleural fluid ADA levels and in case of Tb meningitis CSF fluid ADA was be used so as for Tb Ascites. Cases with respiratory Disease other than tuberculosis were excluded from the study. A serum ADA level of all the cases regardless of the modality of diagnosis was obtained. Serum ADA values cut off was taken as 18U/L, Pleural fluid ADA values cut off was taken as 33U/L, CSF ADA values cut off was taken as 10U/L., Ascites fluid ADA values cut off was taken as 33U/L. Serum ADA levels in apparent healthy subjects were also obtained. The collected data was checked for completeness, accuracy and then entered and analyzed using SPSS 21 using descriptive and inferential statistical tools. The relation between Serum ADA values in patients with tuberculosis and healthy participants cases was analyzed. A p- value of <0.05 was considered significant.

RESULTS

A total of 110 patients including healthy participants were involved in the study of which 35 patients were healthy participants and 75 patients were cases of tuberculosis. There were 51 female patients and 59 male patients. Pleural Fluid TB was the most common type encountered with 36% of the total cases followed by tuberculous Ascites 22% cases. Of the total cases of pulmonary tuberculous included (n=28) only 13 of them showed presence of acid fast bacilli in their sputum while the rest were diagnose based on radiological and other ancillary evidences (Table 1).

Table 1. Distribution of Tuberculosis cases and healthy participants cases in the sample population.

Type of TB	Frequency (%)
Pleural	27 (36%)
Meningitis	3 (4%)
Ascites	17 (22%)
Smear negative pulmonary	15(20%)
Smear positive pulmonary	13(17.3%)
Healthy participants (non TB patients)	35(46.6%)

The mean Serum ADA level of TB patients is 47.0173 and that of Non TB patients is 14.6814. There is a highly significant difference in the mean serum ADA level between TB and non TB patients (p-value < .001) and this level is very high in TB patients concluding that the TB patients have high serum ADA level than non TB patients (Table 2).

Table 2. Mean values of serum ADA between cases and healthy participants.

Presence of TB	n	Mean	Standard Deviation	t-value	p-value
Yes	75	47.0173	16.48101	15.798	< 0.001
No	35	14.6814	4.45821		

Comparisons in the mean Serum ADA level of different types of TB patients was done and the results are summarized as above. There seems to be no any significant difference in the Serum ADA level among different types of TB patients because all p-values in each pair of different TB type's patients are greater than 0.05. However, it showed a significant difference in Serum ADA level of different TB patients with healthy participants group (having no TB) because all P-values

in each pair of healthy participants group and types of TB are less than .05 except in the meningitis group which may be due to low sample size (Table 3).

Table 3. Cross tabulation and comparison between serum ADA values in different groups.

Pair of type of TB	p-value
pleural and meningitis	0.644
pleural and ascites	0.637
pleural and smear negative pulmonary	1
pleural and smear positive pulmonary	0.826
Meningitis and ascites	0.223
Meningitis and smear negative pulmonary	0.696
Meningitis and smear positive pulmonary	0.965
Ascites and smear negative pulmonary	0.731
Ascites and smear positive pulmonary	0.16
smear negative pulmonary and smear positive pulmonary	0.901
Healthy participants and pleural	<0.001
Healthy participants and meningitis	0.161
Healthy participants and ascites	<0.001
Healthy participants and smear negative pulmonary	<0.001
Healthy participants and smear positive pulmonary	<0.001

The mean difference is significant at the 0.01 level.

DISCUSSION

Tuberculosis (TB) remains one of the major public health problems in Nepal with 32474 cases notified and registered at NTP in 2017/18.[13] Despite advances in diagnosis and treatment in TB for the past 60 years, Nepal TB program is missing out to find nearly 28% of estimated cases annually, which has played a big role in healthy participants of TB program. Sputum smear negative and extra pulmonary tuberculosis contribute to a high burden of TB case load in Nepal. For that reason, also, the national Tb guidelines has provided the physicians with a zone for starting Anti tubercular drug therapy based on clinical precision also. Serum level of ADA is a time tested easily and rapidly available blood investigations which literatures have supported may be used as ancillary evidence to validate a clinician's decision to start ATT Ningoth et al. in his observations study comprising of 150 individuals in India compared the serum values of ADA in patients with Diagnosis of pulmonary and Extrapulmonary tuberculosis against 50 age and sex matched healthy participants groups and found a significantly raised ($p < 0.05$) serum ADA concentration in PTB (44.67 ± 3.22) & EPTB (43.63 ± 3.01) compared to healthy participants (13.32 ± 1.97). They suggested that serum Adenosine deaminase (ADA) measurement has good detection potential for PTB & EPTB and can guide the treating physician in doubtful cases to initiate the ATT therapy.[14] Our Findings were also consistent with the above findings such that serum ADA values were found higher in all cases of tuberculosis be it sputum smear positive or negative or even extrapulmonary compared to healthy participants. It was further validated by another study done by Alaarag et al in 2016 involving 70 individuals; 60 patients and 10 healthy healthy participants groups. Serum ADA showed high percentage positivity (90%) in the diagnosis of pulmonary TB with Serum ADA sensitivity and specificity at cut-off point 30.15 µ/l being 95 and 86.7%, respectively, with a positive predictive value of 90.5%, [15.] Another study done in Chandigardh, India by Saini et al in 2018 reported a mean serum ADA (IU/L) of 35.293 in PTB patients and 11.819 ± 8.023 in control groups and found the difference to be highly significant ($P < 0.001$) He further reported a mean serum ADA of 31.107 in sputum positive patients, 39.478 in sputum negative and 11.819 in healthy participants groups with no statistically significant difference observed amongst sputum positive and sputum negative patients Thus, concluded that serum levels of ADA are elevated in both smear negative as well as smear positive cases and thus may be used for diagnosis of tuberculosis [16.] We also in our study did not find any statistical difference between values of Serum ADA in different TB groups compared to healthy participants, thus inferring that serum levels rise in all form of tuberculosis; be it pulmonary or extrapulmonary. Lastly in similar study conducted by Chandar et al in Nepal to validate the credibility of serum ADA , the levels of adenosine deaminase (ADA) in serum in patients with sputum smear negative pulmonary tuberculosis (SNPTB) was compared with serum ADA levels in patients with non-tuberculous pulmonary disease-chronic obstructive pulmonary disease (COPD) and with

healthy participants group They found significantly raised ADA Levels in Tb patients compared to other pulmonary diseases labeling it a promising biomarker.[17]

CONCLUSIONS

Thus this simple study aims to delineate that simple accessible tests like serum ADA levels may may be used as additional supportive evidences in aiding the clinician to diagnose TB in doubtful cases in addition to other microbiological tests so that prompt treatment be started early which may prevent the profound morbidity that may arise with the untreated disease. However further studies are still required to assess its accuracy and validity.

Conflict of interest: None

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