COMPARATIVE ANALYSIS OF CEREBROSPINAL FLUID ADA LEVELS IN TUBERCULOUS AND NON-TUBERCULOUS MENINGITIS

Zahid Ullah, Shazia Nisar*, Waseem Wali*

Combined Military Hospital Banu/National University of Medical Sciences (NUMS) Pakistan, *Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To find out the association of Cerebrospinal Fluid (CSF) adenosine deaminase (ADA) Levels with tuberculosis meningitis.

Study Design: Case control study.

Place and Duration of Study: This study was conducted in the department of Medicine, Pak Emirates Military Hospital, Rawalpindi over a period of six months from May to Oct 2015.

Material and Methods: One hundred and ten participants i.e. 55 cases and 55 controls were included in the study. Lumbar puncture were done and 2cc CSF was obtained. CSF for routine examination and ADA levels were sent to a single lab and pathologist verified report. Based on CSF report, patients were classified as tuberculous meningitis (TBM) and Non- tuberculous meningitis and comparative analysis of ADA level were done in both groups.

Results: Mean age of the patients was 51.33 ± 21.60 and 41.76 ± 18.66 in tuberculosis meningitis and non-tuberculosis meningitis participants. In Tuberculous Meningitis patients, 33 (60.0%) were males while in non Tuberculous Meningitis participants, 35 (63.6%) were males. Mean ADA level in CSF (13.71 ± 4.25 vs. 4.76 ± 3.49, p<0.001), cerebrospinal fluid (CSF) protein level (144.71 ± 99.15 vs 58.27 ± 15.62, p<0.001) and mean cell count (185.00 ± 97.29 vs. 73.71 ± 111.38, p<0.001) were significantly higher in Tuberculous meningitis patients as compared to non Tuberculous Meningitis participants. However, mean glucose was significantly (p<0.001) lower 29.42 ± 8.63 in Tuberculous Meningitis patients in comparison to 57.38 ± 9.13 non-tuberculous meningitis participants.

Conclusion: In conclusion, the estimation of CSF-ADA level is a speedy and simple method, which can be confidently used for diagnosis of tuberculous etiology in TBM patients and differentiating it from non-tuberculous etiology.

Keywords: ADA, CSF, Meningitis, Tuberculous meningitis.

INTRODUCTION

Tuberculosis, a disease of low socioeconomic class, is an endemic disease in developing countries, killing more than 0.5 million people each yearin India alone[1]. Extrapulmonary TB has different types and tuberculous meningitis (TBM) is one of the less frequently observed form. Its incidence rate ranges from 5% to 15%. Although it is not so common, but it is the most serious form of extrapulmonary TB as it has very high rates of morbidity and mortality. The main cause of this high incidence is diagnostic delay and initiation of proper treatment[2,3]. Diagnosis of TBM is usually based on growth of Mycobacterium in cerebrospinal fluid (CSF) and this method is considered as gold standard. CSF acid fast bacilli are rarely identified, with a rate of not more than 10% of the cases. Positivity rate of mycobacterial culture after 8 weeks is very high ranging from 50% to 75%, but the time length to diagnose the tuberculosis is not feasible[4,5]. With advancement of technology, the automated mycobacteria culture system has been introduced but this system does not improve the time for making decisions regarding treatment initiation[6]. Early diagnosis and treatment may be of paramount significance in reducing mortality and sequelae of TBM. Therefore, studies are in

Correspondence: Dr Zahid Ullah, Graded Medical Specialist, Combined Military Hospital Banu Pakistan
Email: dr.zahidkhan82@gmailcom
Received: 12 Apr 2018; revised received: 08 Jun 2018; accepted: 13 May 2018

progress to develop faster and more sensitive diagnostic methods[7]. Adenosine deaminase levels (ADA) are used as marker of cell mediated immunity, especially the ADA levels are markers of T-lymphocyte activation. Many researchers have used it for distinction between tubercular disease and non tubercular disease in ascitic and pleural fluids. CSF ADA levels have been used in many studies as a diagnostic tool for TBM[8]. In a study done in India by Ashok Aggarval, mean CSFADA activity was raised in 57.14% patients with mean CSF ADA levels (9.33 ± 3.08)[9]. The median of ADA activity in meningitis was significantly higher with mean value 22 in in TBM group and 8 in non TBM group. TBM group with mean value of CSF ADA activity 23.05 ± 13.1IU/L showed significantly higher value as compared to non TBM group with mean CSF ADA value of 9.39 ± 5.18IU/L[10]. Karsen *et al* reported that mean CSF ADA levels in tuberculous were 28.34 ± 14.83 IU/L, 8.71 ± 5.83 IU/L in neurobrucellosis, 6.18 ± 2.54 IU/L in purulent meningitis and 3.43 ± 3.48 U/L in aseptic meningitis, when cut off value of ADA levels were kept at 12.35[7]. Currently, TBM and its early diagnosis is a global issue and is becoming more and more crucial especially when CSF routine examination findings are not typical. Relevant studies share the view that ADA can be a useful test in diagnosing TBM. The purpose of this study is to assess use of CSF ADA value in differential diagnosis of TBM as CSF ADA levels is a quick and comparatively cheap diagnostic tool that can be useful, especially in resource-limited settings, in early confirmation of tubercular etiology in cases of meningitis.

MATERIAL AND METHODS

This case control study was started after taking permission from the Hospital Ethics Committee. Informed written consent was taken from all the participants after brief description of the study. The patients of tuberculous meningitis reporting to department of medicine, Pak Emirates Military Hospital, Rawalpindi, were enrolled for cases groups and patients without tuberculous meningitis were selected for control group. The study was carried out over a period of six months from May 2015 to October 2015. The sample size was calculated with the help of WHO sample size calculator using 95% confidence level, 80% power of test, anticipated population means of 9.33 and 28.34 with pooled standard deviation of 3.08[9]. A total of 110 participants were included consisting of 55 patients (of TBM on the basis of modified Ahuja criteria) in cases group and 55 in control group by non-probability consecutive sampling. The participants aged 16-80 years were categorized into cases and controls on the basis of CSF showing increased WBCs. Patients having contraindications for lumbar puncture were excluded from the study. Lumbar puncture was done and 2cc CSF was obtained. CSF for routine examination and ADA levels was sent to a single lab and report was verified by pathologist. On the basis of CSF report, patients were classified as TBM and Non-tuberculous meningitis and comparative analysis of ADA level was done in both groups. Data was entered and analyzed using SPSS version 21. Descriptive statistics were calculated as mean ± SD for quantitative variables and frequency and percentages for qualitative variables. Independent sample t-test was used to compare mean ADA levels in TBM and Non-Tuberculous meningitis. A *p*-value <0.05 was taken as significant.

RESULTS

The mean age of the patients was 51.33 ± 21.60 and 41.76 ± 18.66 in tuberculous meningitis and non-tuberculous meningitis patients. In tuberculous meningitis patients, 33 patients (60.0%) were males while in non tuberculous meningitis participants 35 patients were males (63.6%). In Tuberculous meningitis patients 22 patients (40.0%) were females and in non tuberculous meningitis participants 20 patients (36.4%) were females (table-I). Mean ADA level in tuberculous meningitis patients was 13.71 ± 4.25 and in non tuberculous meningitis participants 4.76 ± 3.49. The mean ADA level was significantly (p<0.001) higher in TBM patients as compared with non-TBM participants. Mean

cerebrospinal fluid (CSF) protein level in tuberculous meningitis patients was significantly (p<0.001) high as compared with non TBM participants. The mean CSF level in TBM patients was recorded as 144.71 ± 99.15 and in non tuberculous meningitis participants as 58.27 ± 15.62. Mean glucose in tuberculous meningitis patients was significantly lower (29.42 ± 8.63 vs 57.38 ± 9.13, p-value <0.001) in comparison to non tuberculous meningitis participants. Mean cell count in tuberculous meningitis patients was noted significantly (p<0.001) higher with mean value of 185.00 ± 97.29 as compared withnon tuberculous meningitis participants having a mean value of 73.71 ± 111.38 given in detail in (table-II).

Table-I: Distribution of age and gender of the patients.

Characteristics	Group A (Tuberculous meningitis)		Group B (Non-tuberculous meningitis)	
	No.	%	No.	%
Age of the patients in categories (Years)				
16-30	15	27.3	18	32.7
31-55	12	21.8	21	38.2
56-80	28	50.9	16	29.1
Total	55	100	55	100
Age of the patients (years)				
Mean ± SD	51.33 ± 21.60		41.76 ± 18.66	
Gender of the patients				
Male	33	60	35	63.6
Female	22	40	20	36.4
Total	55	100	55	100

Table-II: Comparison of ADA, CSF, Glucose and Cell count between both groups.

Group A (Tuberculous Meningitis)		Group B (Non-Tuberculous Meningitis)		p-value
Mean	SD	Mean	SD	
CSF Adenosine Deaminase (ADA) Levels				
13.71	4.25	4.76	3.46	0.001
Cerebrospinal Fluid (CSF) Protein Levels (mg/dl)				
144.71	99.15	58.27	15.62	0.001
Glucose Level (mg/dl)				
29.42	8.63	57.38	9.13	<0.001
Cell Count (cells /mm^3)				
185	97.29	73.71	111.38	<0.001

DISCUSSION

The burden of tuberculous meningitis is high in low socio-economic and developing countries. It has an incidence of 7-12% in under developed countries. The prognosis of these patients become very poor due to delay in diagnosis, which effect the initiation of proper treatment and results in high rate of morbidity and mortality[11,12]. Adenosine deaminase ADA is an enzyme found in purine salvage pathways. Its main function is to catalyze the conversion process of adenosine to inosine and deoxyadenosine to deoxyinosine and ammonia is released in this process. ADA is vital to differentiate lymphoid cells. It is found in active T-lymphocytes and the amount of T-lymphocytes has an inverse relation with degree of differentiation. T-lymphocytes have ten times higher level as compared to erythrocytes. The process of mitogenic and antigenic responses of lymphocytes and T-lymphocytes increases the enzyme activity[13]. Differentiating TBM from non-TBM meningitis especially viral meningitis, by current laboratory methods is a major diagnostic

challenge in clinical practice. The initiation of early treatment improves the outcome in terms of morbidity and mortality. So, urgent diagnosis of TBM is crucial for better prognosis. In this context, diagnostic tests having good sensitivity and specificity, requiring less time for final result, are required[14]. The use of new diagnostic assays has been started in recent years, especially use of molecular techniques including GeneXpert MTB/RIF for diagnosis of extrapulmonary forms of tuberculosis has been started and their clinical utility is required to be further assessed[15,16]. Studies have shown that a cut off value of CSF-ADA above 6 U/l has a high positive likelihood ratio for TBM in patients of meningeal syndrome. In presence of clinical symptoms, this level may be used to initiate the treatment[17,18]. The estimation of CSF-ADA level is useful for diagnosis of TBM as well as to differentiate the TBM from aseptic meningitis[19,20]. In present study, mean ADA level in tuberculous meningitis patients was significantly higher (13.71 ± 4.25) as compared to non tuberculous meningitis participants (4.76 ± 3.49). Mean cerebrospinal fluid (CSF) level in Tuberculous Meningitis patients was significantly (p<0.001) high (144.71 ± 99.15) as compared with non TBM participants (58.27 ± 15.62). Our results are comparable with other studies in which the ADA levels were found to be significantly high in tuberculous meningitis group as compared to non tuberculous meningitis group[4,10]. In another study, it was observed that the CSF ADA value in TBM cases was 16.46 ± 6.24 while in non - TBM cases, it was 5.13 ± 2.96, respectively (highly significant)[22]. Study results reveals that CSF ADA levels were found elevated in TBM patients as compared with non-TBM patients and thus estimating CSF ADA is a useful diagnostic marker in these cases and can help the clinician to make an early diagnosis of TBM[23].

CONCLUSION

It can be concluded that the estimation of CSF-ADA level is a speedy and simple method, which can be confidently used for diagnosis of tuberculous etiology in TBM patients and for differentiating it from non-tuberculous meningitis. Therefore, CSF-ADA level could be used as an investigation tool in resource limited settings for the diagnosis of TBM.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Gupta BK, Bharat A, Debapriya B, Baruah H. Adenosine deaminase levels in csf of tuberculous meningitis patients. J Clin Res 2010; 2: 220-4.
2. Pehlivanoglu F, Yasar KK, Sengoz G. Tuberculous Meningitis in Adults: A Review of 160 Cases. Scientific World J 2012; 2012: 169028.
3. Rashid M, Mushtaq S, Manzoor J, Bhat JA, Chaman S, Hamid A. Comparative analysis of cerebrospinal fluid adenosine deaminase levels in infective meningitis of different aetiologies. Int J Contemp Pediatr 2017; 4: 608-14.
4. Tuon FF, Higashino HR, Lopes MB, Litvoc MN, Atomiya AN, Antonangelo L et al. Adenosine deaminase and tuberculous meningitis - A systematic review with meta-analysis, Scandinavian J Infect Dis 2010; 42: 198-207.
5. Ghosh GC, Sharma B, Gupta BB. CSF ADA determination in early diagnosis of tuberculous meningitis in HIV-Infected patients. Scientifica 2016; 5820823: 1-4.
6. Agarwal S. Study of adenosine deaminase activity as a biochemical marker of cell mediated immunity in tuberculous meningitis, tuberculous pleural effusions andtuberculous ascites. J Med 2012; 13: 32-8.
7. Karsen H, Koruk ST, Karahocagil KK, Calisir C, Baran FC. Comparative analysis of cerebrospinal fluid adenosine deaminase activity in meningitis. Swiss Med Wkly 2011; 141: w13214.
8. Jasani JH, Bhuva KV, Vachhani AV, Patel VR, Sancheti SM, Patel M, et al. Value of adenosine deaminase level for the differential diagnosis various meningitis. Int J Biol Med Res 2012; 3(2): 1644-7.
9. Agarval AK, Bansal S, Nand V. A hospital based study on estimation of adenosine deaminase activity (ADA) in cerebrospinal fluid (CSF) in various types of meningitis. J Clin Diagonost Res 2014; 8: 73-6.
10. Moghtaderi A, Niazi A, Alavi-NainiR, Yaghoobi S, Narouie B. Comparative analysis of cerebrospinal fluid adenosine deaminase in tuberculous and non-tuberculous meningitis. Clin Neurol Neuro Surg 2010; 112: 459-62.
11. Nelson CA, Zunt JR. Tuberculosis of the central nervous system in immunocompromised patients: HIV infection and solid organ transplant recipients. Clin Infect Dis 2011; 53(9): 915–26.
12. Burbelo PD, Keller J, Wagner J, Klimavicz JS, Bayat S, Rhodes S. Serological diagnosis of pulmonary Mycobacterium tuberculosis infection by LIPS using a multiple antigen mixture. BMC Microbiol 2015; 15: 205-14.
13. Tay TR, Tee A. Factors affecting pleural fluid adenosine deaminase level and the implication on the diagnosis of tuberculous pleural effusion: a retrospective cohort study. BMC Infect Dis 2013; 13: 546-9.
14. Chacko F, Modi M, Lal V, Prabhakr S, Rana SV, Arora SK. Diagnostic efficacy of adenosine deaminase levels in cerebrospinal fluid in patients of tubercular meningitis: A

comparison with PCR for Mycobacterium tuberculosis. Annals Neurosci 2010; 17(3): 126-30.
15. Hillemann D, Rusch-Gerdes S, Boehme C, Richter E. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. J Clin Microbiol 2011; 49: 1202–5.
16. Ioannidis P, Papaventsis D, Karabela S, Nikolaou S, Panagi M, Raftopoulou E, et al. Cepheid GeneXpert MTB/RIF assay for Mycobacterium tuberculosis detection and rifampin resistance identification in patients with substantial clinical indications of tuberculosis and smear-negative microscopy results. J Clin Microbiol 2011; 49: 3068–70.
17. Solari L, Soto A, Agapito JC, Acurio V, Vargas D. The validity of cerebrospinal fluid parameters for the diagnosis of tuberculous meningitis. Int J Infect Dis 2013; 17: 1111–5.
18. Barua R, Hossain MA. Adenosine deaminase in diagnosis of tuberculosis: A review. Anwer Khan Mod Med Coll J 2014; 5(2): 43-8.
19. Chacko F, Modi M, Lal V, Prabhakar S, Rana SV, Arora SK. Diagnostic efficacy of adenosine deaminase levels in cerebrospinal fluid in patients of tubercular meningitis: A comparison with PCR for Mycobacterium Tuberculosis. Ann Neurosci 2010; 17(3): 126–30.
20. Shinde AR, Ghorpade KS, Siddiqui AM. A study of Cerebrospinal Fluid Adenosine deaminase and C-reactive protein in Bacterial, Tubercular and Viral meningitis. Asian J Biomed Pharma Sci 2015; 5(44): 15-8.
21. Tyler KL. A history of bacterial meningitis. Hand B Clin Neurol 2010; 95: 417-33.
22. Chander A, Shrestha CD. Cerebrospinal fluid adenosine deaminase levels as a diagnostic marker in tuberculous meningitis in adult Nepalese patients. Asian Pac J Trop Dis 2013; 3(1): 16-9.
23. Gupta BK, Bharat A, Debapriya B, Baruaha H. Adenosine deaminase levels in csf of tuberculous meningitis patients. J Clin Med Res 2010; 2(5): 220-4.