Original Research Article

Adenosine deaminase activity in cerebrospinal fluid for diagnosis of tuberculous meningitis

K P Shiyas[1], Sam Varghese[2*], A Abdul Majeed[3]

[1]Associate Professor, Department of Paediatrics, Al Azhar Medical College, Thodupuzha, INDIA.
[2]Associate Professor, Department of Paediatrics, Snims, Chalakka, Kunnukara, Ernakulam, Kerala, INDIA.
[3]Consultant Paediatrician and Neonatologist, Craft Hospital And Research Center Kodungalloor, INDIA.
Email: sami3304@yahoo.com

Abstract

Background: Tuberculosis is a heavy burden for both the industrialized and developing countries. Among the total of cases infected, 95% occur in developing countries alone. Neurotuberculosis is one of the serious complications of primary tuberculosis infection. Tuberculous meningitis (TBM) is the main cause of death and disability in children with tubercular disease**.** In this study adenosine deaminase (ADA) activity of CSF and its usefulness as a diagnostic aid in TBM was studied in detail**. Methods:** All India Institute of Medical Science (AIIMS) criteria was used for the diagnosis of TBM. CSF ADA activity was estimated by spectrophotometry. Spectral-line photometer for accurate measurements at wavelengths between 620 and 650nm was used. **Results**: The high level of CSF ADA activity in tuberculous meningitis compared to other groups was found to be statistically significant ($p < 0.001$). Correlation of ADA value with protein levels in CSF showed increase in the ADA activity in proportion to the increase in protein levels. With a cut off value of 7.0 U/L sensitivity of CSF ADA value in diagnosing TBM was 91.6% with a specificity of 75%. **Conclusion**: CSF ADA estimation is useful in diagnosing TBM as well as in differentiating tuberculous meningitis from pyogenic meningitis. Estimation of CSF ADA is a simple, rapid and cheap procedure that may include in the routine investigation of tuberculous meningitis
keywords: Adenosine deaminase, Cerebrospinal fluid, Neurotuberculosis, Tuberculous meningitis

***Address for Correspondence:**
Dr Sam Varghese, Associate Professor, Department of Pediatrics, SNIMS, Chalakka, Kunnukara, Ernakulam, Kerala, INDIA.
Email: sami3304@yahoo.com
Received Date: 03/11/2020 Revised Date: 13/12/2020 Accepted Date: 19/01/2021
DOI: https://doi.org/10.26611/10141723

Access this article online

Quick Response Code:

Website: www.medpulse.in

Accessed Date: 22 February 2021

INTRODUCTION

Tuberculosis long known to be, a major cause of morbidity and mortality throughout the world, has for the several decades been a neglected disease in both the industrialized and the developing countries. It is the largest cause of death from a single infectious agent in the world[1]. Tuberculosis is now attracting renewed interest due to HIV endemicity in various countries[2], proven effectiveness of short-course chemotherapy and the realization that, tuberculosis control is one of the most cost-effective health interventions in developing countries[3]. About 1700 million people (1/3rd of world's population) are infected with tuberculosis. Out of which 95% are in the developing world. About 3 million cases die every year with an addition of 4-5 million new cases every year[4]. According to the studies conducted by National Institute of Tuberculosis (NIT) Bangalore, 2.1% of the children under 5 years have primary tuberculosis infection, giving an estimate of 1.9 million getting infected every year. Among all the paediatric admissions, 6 – 10% are due to tuberculosis. Majority of them have serious diseases like meningitis, miliary disease or severe pulmonary involvement. Neurotuberculosis is one of the serious complications of primary tuberculosis infection. Tuberculous meningitis (TBM) is the main cause of death and disability in children with tubercular disease[5]. Study done by Dhariwal and Udani showed Neurotuberculosis was responsible for 9.6% of the admissions and 10% of the mortality[6]. As per many studies in India, 70 – 75% of TBM

How to cite this article: K P Shiyas, Sam Varghese, A Abdul Majeed. Adenosine deaminase activity in cerebrospinal fluid for diagnosis of tuberculous meningitis. *MedPulse International Journal of Pediatrics.* February 2021; 17(2): 23-28.
http://medpulse.in/Pediatrics/index.php

cases occur in children below 5 years, while 25 – 30% occur in 5 years and above. Mortality in TBM varies from 15-75%[7,8,9]. As the cerebrospinal fluid (CSF) seldom reveals acid fast bacilli (AFB) on smear examination, and culture results take about 8 weeks, there is an urgent need for a rapid diagnostic test for confirming the diagnosis of TBM. The ideal diagnostic test, with an adequate sensitivity and an acceptable specificity, which is also cheap and easy to carry out in the field settings, is yet to be developed. Estimation of CSF adenosine deaminase (ADA) has been found to have a sensitivity range of 60 – 100% and specificity range of 84 – 99% in various studies[10,11,12,13]. Further studies are required for distinguishing TBM from other forms of meningitis with CSF adenosine deaminase estimation. In this study ADA activity and its usefulness as a diagnostic aid was studied in detail. An attempt was made for early diagnosis of TBM based on adenosine deaminase activity in CSF.

MATERIALS AND METHODS

The material for the present study was collected from JSS Medical College, Mysuru. 24 cases of TBM which were admitted were taken for the present study. For comparison, 20 cases of pyogenic meningitis and another 20 cases with normal CSF analysis were taken.

All India Institute of Medical Science (AIIMS) criteria was used for the diagnosis of TBM. i.e, Demonstration of acid-fast bacilli in the CSF or fulfilment of the following criteria:

(A) Essential

CSF showing

(i) Predominant lymphocyte pleocytosis > 50/mm^3

(ii) Protein > 60 mg%

(iii) Sugar <2/3rd of blood sugar

(B) Supportive

Along with essential criteria, two or more of the following clinico-investigational criteria:

(i) History of fever for two weeks or more

(ii) Positive family history of tuberculosis

(iii) Mantoux test (5TU) > 10 mm

(iv) Positive radiological evidence of tuberculosis elsewhere in the body

(v) CT scan evidence of basal exudates or CNS tuberculosis

(vi) Isolation of AFB from gastric lavage or other sites

(vii) Histologically proven tubercular lymphadenitis

Criteria for diagnosing pyogenic meningitis

Pyogenic meningitis was diagnosed on the basis of clinical presentation, CSF analysis, Gram's stain and culture studies. Controls were taken on the basis of normal CSF studies. Out of 20 cases enrolled 6 were febrile convulsions, 7 were hypocalcemic convulsions, 5 cases were seizure disorders and 2 were gastroenteritis with dyselectrolemia. After selecting the cases a detailed history and clinical examination including fundoscopic examination were done as per the proforma. Patients with TBM were classified into three stages, as described by the British Medical Council Staging System. Following investigations were done – Hb, TC, DC, Mantoux test, Sputum/gastric aspirate for AFB, Chest X rays, Skull x ray and CT scan (relevant cases) and CSF examination. CSF ADA activity was estimated by spectrophotometry. Spectral-line photometer for accurate measurements at wavelengths between 620 and 650nm was used. Data was collected in Microsoft Excel and analysed using SPSS version 16. All study variables were analysed using descriptive statistical methods like frequencies and percentages for categorical variables and mean with standard deviation for continuous variables. Students t test was done to find the significant associations and sensitivity and specificity were also calculated.

RESULTS

Present study showed equal distribution of cases among both the sexes (12 males and 12 females). Maximum cases were below 4.5 years, constituting 50% of total. Youngest child in the present study was 6 months old and oldest was 12 years old. The mean age among males was 5.5 (± 3.8) years, while among females, the mean age was 6.1 (± 4.1) years. Put together the mean age for both sexes were 5.8 (± 3.9) years. History of contact with tuberculosis was elicited in 9 cases (37.5%). Previous history of measles within 6 months of the presenting complaints was obtained only in one case (4.2%). Two patients had history of chronic otitis media (8.3%). In the present study, there were 7 unimmunized children who had not received BCG vaccination (29.2%). All the patients in the study group had fever as the presenting symptom. Altered sensorium was the second most common symptom (79.2%). Headache was not seen in younger children, but it was a common finding in children above 5 years of age. History of headache was elicited in 15 cases (62.5%). Vomiting and convulsions were seen in majority of the cases. Irritability was a common symptom in younger children (10 cases) followed by refusal of feeds (6 cases). In the present study nutritional status of the patients was graded according to the IAP classification. Only four patients were nutritionally normal. Nine cases (37.5%) belonged to grade III or grade IV malnutrition. All patients were from low socioeconomic group except 2 patients who belonged to Class II of modified B.G Prasad's classification. Majority of the patients were admitted in stage III of the disease (50.0%). Only 2 patients presented in the early course of

the disease. Most common sign elicited on admission were signs of meningeal irritation (87.5%) followed by Macewen's sign (45.8%). Eleven cases had hemiplegia/hemiparesis (45.8%). Same number of cases had cranial nerve deficit. Most common abnormal finding in fundoscopy was papilloedema. Majority of the patients in the present study had haemoglobin levels between 9 – 12 g/dl. Leucocytosis (TC > 14,000) was seen in 8 cases (33.3%). ESR was raised in all the cases and was above 40 mm at the end of 1 hour in 13 cases (54.2%). Chest X rays were abnormal in 9 cases (37.5%). Out of which four cases had bronchopneumonia. Other abnormal findings in chest X-ray were Hilar lymphadenopathy (2 cases) and paratracheal lymphnodes (1 case). Mantoux test was done in all cases. It was positive in 7 cases (29.2%). Majority of negative Mantoux tests were seen in stage III disease and grade IV malnutrition. CT scan was done in only 14 patients out of 24 TBM cases enrolled in the study. Most common findings in CT were cerebral oedema (42.9%), hydrocephalus (35.7%) and infarction (35.7%). CT scan showed normal findings in 2 cases (14.3%). Other findings were Gyral enhancement (7.1%) and tuberculoma (7.1%). CSF pressure was increased in 13 cases (54.2%). Majority of the cases had clear CSF (62.5%). Cell count was elevated to the range of 50 – 300/mm^3 in 79% of the cases. Cob-web formation was noticed in 2 out of 24 cases. Samples were kept and used to prepare dry smears and stained with Z N stain. AFB was not demonstrated. All samples were stained for AFB and also cultured for tubercle bacilli in L.J media. There was no growth. CSF protein value was in the range of 101 – 200 mg/dL among more than half of the patients in the present study group. Seventeen cases (70.8%) showed low glucose level (<40mg/dL) in cerebrospinal fluid. Maximum deaths were in patients presented with stage III TBM. Six cases died out of 12 (50%). There were 2 deaths out of 10 in patients with stage II disease. There were no deaths in patients who presented early. Overall mortality rate in this study group was 33.3%. High mortality was seen in patients with grade III and grade IV malnutrition. Seven out of 8 deaths occurred in grade II to grade IV malnourished children.

Table 1: ADA activity levels of different groups

Group	Total number of cases	CSF – ADA levels in U/L		
		Mean	S.D.	Range
Tuberculous meningitis	24	13.1	3.5	6.2 – 19.6
Pyogenic meningitis	20	6.6	2.4	3.2 – 12.8
Controls (Normal CSF)	20	1.6	0.6	0.8-3.2

CSF adenosine deaminase levels were estimated in tuberculous meningitis, pyogenic meningitis, and controls (normal CSF). ADA activity in tuberculous meningitis group was significantly elevated with a mean value of 13.1 ± 3.5 U/L compared to pyogenic meningitis group (mean = 6.6 ± 2.4) and control group (mean = 1.6 ± 0.6). Highest ADA activity in TBM group was 19.6 U/L compared to pyogenic meningitis (12.8 U/L) and control (3.2 U/L). Lowest activity in TBM group was 6.2 U/L (Table 1).

Table 2: Table showing t values and p values

Category	t value	p value	Inference
TBM vs PM	7.26	<0.001	Significant
TBM vs Control	14.42	<0.001	Significant
PM vs Control	9.07	<0.001	Significant

The high level of CSF ADA activity in tuberculous meningitis compared to other groups was found to be statistically significant (p <0.001) (Table 2). As mean of CSF-ADA activity in pyogenic meningitis is 6.6 U/L we took more than 7 as the cut-off value for diagnosis of TBM. Using a cut off value of 7 U/L the sensitivity of CSF ADA for diagnosing tuberculous meningitis was 91.6%, while the specificity was 75.0%. Using the same cut-off, predictive value of positive test was 0.814, while predictive value of negative test was 0.882. Using a cut off value of 8 U/L sensitivity was 91.6%, but the specificity of the test increased slightly to 80.0%. Positive predictive value was 0.846 and negative predictive value was 0.888.

Table 3: Table showing CSF ADA activity vs CSF protein levels in tuberculous meningitis

CSF protein in mg/dL	Total number of cases	CSF ADA in U/L		
		Mean	S.D	Range
<100	5	8.2	2.0	6.2 – 11.2
101 – 200	13	13.6	1.9	10.0 – 17.0
>200	6	16	3.1	11.0 – 19.6

Correlation of ADA value with protein levels in CSF showed increase in the ADA activity in proportion to the increase in protein levels. Five cases had protein level less than 100mg/dL with a mean ADA level of 8.2 ± 2.0. maximum cases (13) had protein level between 100 – 200 mg/dL with mean ADA level of 13.6 ± 1.9. Six cases had protein level more than 200 mg/dL with mean ADA level of 16 ± 3.1. All were statistically significant (p<0.05) (Table 3).

Table 4: Table showing CSF ADA activity vs CSF glucose levels in tuberculous meningitis

CSF glucose in mg/dL	Total number of cases	CSF ADA in U/L		
		Mean	S.D	Range
Below 40	17	13.0	3.8	6.2 – 19.6
Above 40	7	13.3	2.8	9 – 17.5

Seventeen cases had CSF glucose level less than 40 mg/dL with CSF ADA level 13.0 ± 3.8. Seven cases showed CSF glucose level more than 40 mg/dL with a mean CSF ADA level of 13.3 ± 2.8. This was not statistically significant (p >0.1) (ADA activity does not correlate with CSF sugar levels) (Table 4).

Table 5: Table showing CSF ADA level vs CSF lymphocyte count in tuberculous meningitis

Lymphocyte count/mm³	Total number of cases	CSF ADA in U/L		
		Mean	S.D	Range
<100	9	11.8	2.8	6.2 – 15.4
100 – 300	13	13.5	3.8	6.8 – 19.6
>300	2	16.8	1.2	15.6 – 18.0

Correlation of ADA value with CSF lymphocyte count showed increase in ADA activity in proportion to the increase in lymphocyte count. Maximum cases (13 out of 24) had CSF lymphocyte count between 100 – 300/mm^3 with mean ADA value of 13.5 ± 3.8. Correlation between the groups with a cell count below 100/mm^3 (A) and above 300/mm^3 (C) were statistically significant ($p < 0.05$). But the other groups did not correlate statistically ($p > 0.1$) (Table 5).

DISCUSSION

This study was a prospective study of 24 cases of tuberculous meningitis in children conducted at J.S.S Hospital, Mysore from March 2012 to February 2014. Maximum incidence of TBM noted in the present study was below 5 years, 54.16%. Higher incidence was seen in studies conducted by Udani *et al.*,[14] and D.G. Benakappa *et al.*,[15], (86.0%). This may be due to higher coverage of BCG vaccination. Present study showed equal distribution of cases with male to female ratio of 1:1. This is in accordance with ratio observed by Ahuja *et al.*,[16] (1.1:1). Higher incidence in males is reported by D.G. Benakappa *et al.*, (1.5:1)[15]. In the present study higher incidence of TBM was noted in children with grade III and grade IV malnutrition. More than one third (9 cases) belonged to grade III and IV malnutrition. This is because most of our patients were from rural areas where illiteracy and poverty prevail. History of contact was elicited in 9 cases (37.5%). The results are comparable with that of R.K. Garg *et al.*, (50.0%)[17]. Other studies showed varying incidence of contact history. Hence careful history taking is essential in any meningitis case. It may clinch the diagnosis. The presenting symptoms in the present study is comparable with studies conducted by P.M Udani *et al.*, and D.G Benakappa *et al.*,[14,15]. Fever was the presenting symptom in all 24 cases (100%). Benakappa *et al.* reported similar findings (98%) in his series[15]. Convulsions were noted in 50% of the patients enrolled in the present study. Similar observations were made by Udani *et al.*, (47%)[14]. In the present study vomiting was present in 14 cases (58.3%) slightly higher than the observation made by Udani *et al.*, (42%)[14]. But higher incidence of vomiting was also observed by Mohapatra *et al.*, (60%)[18] and Kennedy *et al.* (71%)[19]. Altered sensorium was the second commonest symptom in the present study. Similar observations were made by Ahuja *et al.*, (83%)[16]. Cough was present in 8 cases (33.3%). Similar observations were made by Kennedy *et al.*[19]. In the present study, headache was present in 15 patients with TBM (62.5%). Similar observations were made by Kennedy *et al.* (73%)[19] and Mohapatra *et al.* (66%)[18]. Most of the signs are comparable with other studies. Incidence of meningeal signs are high because most of the children 21 out of 24 are above the age of 2 years. Many had hemiplegia/paresis and cranial nerve involvement as many cases presented in the advanced stage of the disease. No cases of choroid tubercles were detected, whereas P.M Udani *et al.*, have reported 1.2% in their study[14]. Abnormal x ray findings in the present series (37.5%) are comparable with Benakappa *et al.*[15]. Incidence of military tuberculosis in the present study is zero, when compared with Udani (17.6%) and Benakappa *et al.* (2.0%)[14,15]. Radiographic studies demonstrated abnormal chest findings in as many as 87% in a western study (Yaramis *et al.*,)[20]. Positive Mantoux test was seen in 7 cases (29.2%). Similar observations were made by Benakappa *et al.* and Yaramis *et al.*,[15,20]. In the present study 14.2% of CT findings were normal. Similar findings were made by Ozates *et al.*[21]. Higher incidence of hydrocephalus (80%) was observed in Western study whereas higher incidence of cerebral oedema and infarction (42.8%) were seen in the present study. Ozates *et al.*, observed these findings in a large study group (n = 289) when compared to small group (n = 14) of the present study[21]. This may be the reason for not correlating well with reference study. Majority of patients CSF protein was between 50 – 200 mg%. This is in accordance with the findings of G.C. Upadhyaya *et al.*, and S.K Khanna *et al.* Decreased CSF sugar was seen in 70.8% of cases. Ford *et al.*, reported that CSF sugar was normal at onset and later on decreased to 15 – 25 mg%. No similar observations were made in the present study. In 50% of cases, cells were in the range of 100 – 300/mm^3. Cell types were predominantly lymphocytes. Similar observations were made by G.C Upadhyay *et al.*[22] and P.M Udani *et al.*[14]. In the present study AFB was not seen and was negative in culture. This is due to the fact that CSF was stained without centrifugation. Use of fluorescent acid-fast staining (Rhodamine or Auramine) and examination of several samples over a few days will give better yield. Udani *et al.*, reports 30% positive for AFB[14] and A.K Shah *et al.*, reports 12.5% [8]. The above data indicates progressive decrease in the mortality in TBM cases. This is due to better understanding of the disease and improved management. Present study shows better outcome in all stages of the disease when compared to Tuberculosis Research Centre (TRC), Chennai series. AIIMS, New Delhi series showed better outcome in all three stages when compared to other two studies. In the present study, CSF ADA levels were elevated in all the cases of

tuberculous meningitis with a mean of 13.1 ± 3.5 (range 6.2 – 19.6) when compared to pyogenic meningitis and controls, the difference being statistically significant ($p < 0.001$). The results of the present study with respect to tuberculous meningitis correlate with that of M.A. Piras *et al.*[23]. In the present study, CSF ADA activity increased with increase in protein level (statistically significant). Mohapatra *et al.*, and R Prasad *et al.*, also report an increase in the CSF ADA activity in relation to rise in CSF protein levels but mean CSF ADA value in present study is high compared to other studies[18,24]. This could be due to laboratory or geographical factors. In the present study, CSF ADA value shows no correlation with the CSF sugar levels. This finding is consistent with the observations made by Mohapatra *et al.*, and R. Prasad *et al.*,[18,24]. In the present study CSF ADA activity increased with an increase in CSF lymphocyte count (as given in table 13e). But only group with less than 100 lymphocytes/mm^3 and group with more than 300 lymphocytes/mm^3 showed statistically significant correlation ($p<0.05$). Mohapatra *et al.*, and R Prasad *et al.*, also have reported an increase in CSF ADA in relation to CSF lymphocyte count[18,24]. With a cut-off value of 8.0 U/L, the sensitivity of CSF ADA for diagnosing tuberculous meningitis was 91.6% while specificity increased to 80%. As mean of CSF ADA activity in pyogenic meningitis was 6.6U/L we took more than 7 as cut-off value for diagnosis of TBM in the present study. In spite of using different cut-off values results correlates with that of Mohapatra *et al.* Gold standard of Tuberculous meningitis diagnosis (isolation of AFB/Demonstration of AFB) was not achieved in any cases. Diagnosis of TBM was made on the basis of clinical criteria. Other rapid diagnostic tests like PCR, ELISA were not used. CSF ADA estimation was done only once. Hence CSF ADA response to therapy could not be established.

CONCLUSION

CSF ADA activity showed significant elevation in all cases of tuberculous meningitis, with more than 90% of the patients having CSF ADA activity more than 7 U/L. With a cut-off value of 7.0 U/L sensitivity of CSF ADA value in diagnosing TBM was 91.6% with a specificity of 75%. CSF ADA estimation is useful in diagnosing TBM as well as in differentiating tuberculous meningitis from pyogenic meningitis. Estimation of CSF ADA is a simple, rapid, and cheap procedure that can be included in the routine investigation of tuberculous meningitis.

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Source of Support: None Declared
Conflict of Interest: None Declared