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Original Research Article

Adenosine deaminase activity in cerebrospinal fluid: diagnostic investigation in central nervous system disorders in children

Sk Rafikul Rahaman[1]*, Anshuman Panda[2], Pradyut K. Mandal[1], Kripasindhu Chatterjee[1], R. V. Borgaonkar[3]

[1]Department of Pediatrics, [2]Department of General Surgery, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal-721645, India
[3]Department of Pediatrics, Government Medical College, Aurangabad, Maharastra-431001, India

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***Correspondence:**
Dr. Sk Rafikul Rahaman,
E-mail: rahamanrafikul01@gmail.com

ABSTRACT

Background: Tubercular meningitis (TBM) is an endemic disease in developing countries. Adenosine deaminase activity (ADA) has been of great importance for many years in TBM diagnosis. The objective of this study was to determine the CSF-ADA levels in different CNS disorders, to compare the CSF-ADA activity in different types of meningitis, to find out the sensitivity and specificity of CSF-ADA in the diagnosis of TBM and to establish the prognostic value of CSF-ADA in TBM in comparison to Control group.
Methods: For control group CSF was collected from the patients of simple febrile convulsions and idiopathic epilepsy.
Results: The present study was carried out in the 112 cases of different CNS disorders, age ranging from 4 months to 12 years with a mean age of 4.12 years and 38 cases (27+11) of control group (simple febrile convulsion and idiopathic epilepsy). In the present study CSF-ADA level was statistically significantly increased in all types of meningitis ($p<0.05$). In case of TBM, the mean CSF-ADA level increased statistically significantly with increase in CSF protein level ($p<0.05$). In case of TBM, there was no significant difference in the mean ADA value according to CSF sugar level ($p<0.10$). In case of TBM, the mean CSF-ADA level increased significantly with increase in CSF cell count ($p< 0.01$) mainly lymphocytes.
Conclusions: Thus it can be concluded from our study that CSF-ADA estimation is relatively simple and inexpensive procedure in the early diagnosis of tuberculous meningitis with high sensitivity (100%) and specificity (97.5%) at a cut-off level of 5IU/L and can be used in differentiating TBM from other types of meningitis. Along with diagnostic utility of CSF-ADA, it has also prognostic value in the follow-up case of tuberculous meningitis.

Keywords: Adenosine deaminase, CNS, Children, Tuberculous meningitis

INTRODUCTION

Adenosine deaminase exists in multiple molecular forms in human tissue. One form of the enzyme appears to be "particulate". Three forms of the enzyme are soluble and inter-convertible with apparent molecular weights of approximately 36,000, 114,000, and 298,000 (designated small, intermediate, and large, respectively). Adenosine deaminase (ADA) catalyses the irreversible hydrolytic deamination of adenosine to produce ionosine and ammonia.[1]

Adenosine + H2 O = Ionosine + NH3

Principal biological activity of ADA is detected in T lymphocytes.[2] The enzyme activity is inversely

proportional to the degree of T cell differentiation.[3] Increased levels plasma ADA has been observed in certain infectious diseases with an active participation of cell mediated immune responses.[4] Specific activity of this enzyme is higher in T lymphocytes than B lymphocytes.[5] It is secreted by T lymphocytes and macrophages during infections. So there has been interest in ADA as a marker of chronic inflammatory conditions such as tuberculous meningitis.[6]

Tuberculosis (TB) is one of the leading causes of mortality and morbidity in developing countries. The best estimate is that there were 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among HIV-positive people. In terms of cases, the best estimates for 2015 are that there were 10.4 million new TB cases (including 1.2 million among HIV-positive people), of which 5.9 million were among men, 3.5 million among women and 1.0 million among children. Overall, 90% of cases were adults and 10% children, and the male: female ratio was 1.6:1.7 Tuberculous meningitis (TBM) is an endemic disease among socioeconomically disadvantaged communities in both developing and developed countries.[7]

Tuberculous meningitis (TBM) still remains an important cause of morbidity and mortality in India due to lack of early and timely diagnosis. Even when it is not fetal, early and correct treatment is essential for successful outcome in patients of tuberculous meningitis.[8]

Tuberculous meningitis continues to confront clinicians with a diagnostic problem. Acid fast bacilii may be difficult to find in the cerebrospinal fluid (CSF) on ziehl - Neelseen staining, while culture of Mycobacterium Tuberculosis from CSF may take from 6-12 weeks. Confirmation of diagnosis may be particularly difficult in children where only small amount of CSF may be submitted for examination and culture.

Haas F et al has reported positive only in 10-40% of patients and cultures are positive in 45-90% depending upon the quality of CSF and laboratory facilities.[9] Workers from tropic countries, attain bacteriological proof in only 10-20% of cases.[10]

Levels of ADA in CSF are known to be increased in TBM.[11] It has been suggested by Piras and Gakis that ADA levels in CSF may help to differentiate tuberculous meningitis from "viral lymphocytic meningitis" and further that tuberculous meningitis and bacterial meningitis "differ clearly from one another regards the relationship of ADA to the number of cells".[12,13] ADA activity has been shown to be high in nervous system neoplasia.[11] Many workers have shown increased CSF-ADA values during acute inflammatory neuropathies and various forms of meningitis, whereas Hirschhorn et al have reported that deficiency of ADA may lead to neurological abnormities.[14] Diagnostic relevance to CSF-ADA activity in patients suffering from nervous system neoplasia and on the other hand they found a low enzymatic activity in the course of non-neoplastic neurological diseases. High values were also met by Kluge et al during acute inflammatory cerebropathies, atrophy and neoplasia of nervous system.[12,15]

As very less studies are available regarding CSF-ADA activity in different types of meningitis and other neurological disorders, CSF-ADA activity is carried out here in patients suffering from tuberculous meningitis, bacterial meningitis, aseptic meningitis and various other neurological disorders and results are compared.

METHODS

The present prospective observational study was done with the participants (below 12 years of age) of various central nervous system disorders admitted in the paediatric wards, Government Medical College and Hospital, Aurangabad after taking institutional ethics committee permission. For control group CSF was collected from the patients of simple febrile convulsions and idiopathic epilepsy.

Inclusion criteria

- Child below 12 years of age
- Clinically suspected cases of meningitis
- Child with symptoms and signs suggestive of CNS involvement (other than simple febrile convulsions idiopathic epilepsy).

Exclusion criteria

- Child who had received antimicrobial therapy before admission
- Child who had received anti-tubercular drug therapy before admission.

Criteria for control group

- Clinical features suggestive of febrile convulsion
- Features suggestive of idiopathic epilepsy

Diagnostic criteria of tuberculous meningitis[10]

(H/O) contact known case of active tuberculosis; onset is insidious; presence meningeal sign, positive tuberculin test- induration 10mm or more than that; X-ray chest: evidence of hilar lymphadenopathy, or primary complex or military TB. CSF examination shows pressure raised; clear/cob-web formation of appearance on standby; cell count less or equal than 500/mm^3 with lymphocytic predominance and in early cases predominance of polymorphonuclear leucocytes. Z.N staining shows presence of acid fast bacilii and positive culture for AFB. Biochemical changes like CSF glucose is less than 40 mg/dl or half the value of simultaneous blood glucose level; protein concentration is normal or slightly elevated

(100-300 mg/dl) during early stage and later may be more high.

Standard diagnostic criteria of acute bacterial meningitis, aseptic meningitis, encephalitis, brain tumors, acute febrile hemiplegia, neurodegenerative disorders, enteric encephalophy, acute cerebelletis, cerebral malaria, cerebral palsy, Guillain-Barré syndrome, simple febrile convulsion, and Idiopathic epilepsy were assessed for exclusion of other differential diagnosis.[16-29]

Estimation of parameters

Hemoglobin, total leucocyte count, differential leucocyte count, malaria parasite, blood culture, widal test, tuberculin test, radiological (done in cases where needed) were done. CSF examination;

- Physical examination-to differentiate between clear, turbid and cob-web formation on standing
- Biochemical estimation.

Collected in plain vial for

- CSF Protein- by turbidity method using 3% sulphosalicylic acid
- CSF Sugar –by GOD-POD method
- CSF Chloride by silver staining method.

Cytology

The CSF was collected in sterile plain bulb and a drop of CSF under coverslip was examined under microscope for presence of cells. total count of cells was done by using Neubauer`s chamber. The CSF was centrifuged at 1500 rpm for 5 mints and sediment was smeared and stained with Leishman`s stain and Gram`s stain and observed carefully for the type of cells and bacteria. Sediment was also examined for acid fast bacilii after staining it was Ziehl Neelsen (Z.N.) stain.

CSF was also collected in sterile plain bulb and sent for culture of routine bacteria and for AFB on Lowenstein-Jensen (L.J.) media. CSF was examined for malignant cells whenever indicated by staining the smear with papanicolaou`s stain.

CSF-ADA estimation

Fresh CSF sample was collected in heparinized vial and estimation was done by colorimetric method using Beckman-spectrophotometer at optimum wave length of 628 mm (620 nm to 650 nm) and at a temperature of 370C as per the method described by Giusti.[30] The capture data was analysed using descriptive statistics.

RESULTS

A total number of 112 cases of different central nervous system disorders and 38 control (simple febrile convulsion and idiopathic epilepsy) were studied in patients attending Pediatric Department at tertiary care teaching Hospital, Aurangabad. The youngest patient was of 4 months and the eldest one of 12 years. Mean age was 4.12 years.

Table 1: Age distribution of the patients (n = 112).

Age in years	No. of cases	Percentage
0-1	30	26.87
1-2	14	12.50
2-3	11	09.83
3-4	08	07.15
4-5	09	08.04
5-6	15	13.39
6-7	04	03.58
7-8	06	05.35
8-9	06	05.35
9-10	07	06.25
10-11	01	00.89
11+	01	00.89
Total	**112**	**100**

Table 2: Age distribution of the control group (n = 38).

Age in years	No. of cases	Percentage
0-1	10	26.31
1-2	11	28.94
2-3	04	10.52
3-4	05	13.15
4-5	04	10.52
5-6	--	--
6-7	01	02.63
7-8	01	02.63
8-9	--	--
9-10	01	02.63
10-11	--	--
11+	01	02.63
Total	**38**	**100**

Table 3: Age distribution in the patients of TBM (N = 32).

Age in years	No. of cases	Percentage
0-1	15	46.88
1-2	06	18.75
2-3	03	09.38
3-4	--	--
4-5	04	12.50
5-6	02	06.25
6-7	01	03.12
7-8	01	03.12
8-9	--	--
9-10	--	--
10-11	--	--
11+	--	--

Table 4: Sex distribution of patients and control group.

Sex	No. of cases	Percentage
Case		
Male	65	58.03
Female	47	41.97
Control		
Male	26	68.42
Female	12	31.58

Majority of children different CNS disorders were between the ages of 4 months to 6 years (77.67%) (Table 3). The youngest patient was of 4 months and eldest was of 12 years with the mean age 4.12 years. In the control group majority of children were between the ages 6 months to 5 years (89.47%). The youngest one was of 6 months and the eldest of 12 years with the mean age 2.99 years. Highest incidence of tuberculous meningitis was between 7 months to 5 years of age (87.5%).

Table 5: Distribution of patients of different CNS disorders.

Diseases	No. of cases	Percentage
Tubercular meningitis	32	28.57
Acute bacterial meningitis	19	16.96
Aseptic meningitis	10	08.93
Encephalitis	16	14.29
Brain neoplasm	02	01.79
Acute infantile hemiplegia	07	06.25
Neurodegenerative disorders	03	02.68
Enteric encephalopathy	05	04.46
Acute cerebelletis	04	03.57
Cerebral malaria	08	07.14
Cerebral palsy	04	03.57
Guillian Barre` syndrome	02	01.79

Male to female ratio in patients of different CNS disorders were 1.38:1, suggesting apparent male predominance (Table 4). In TBM cases male to female ratio was 1.29:1. Study groups comprised of 32 cases of TBM, 19 cases of acute bacterial meningitis, 10 cases of aseptic meningitis, 16 cases of encephalitis, 2 cases of brain neoplasm, 7 cases of acute infantile hemiplegia, 3 cases of neurodegenerative disorders, 5 cases of enteric encephalopathy, 4 cases of acute cerebelleritis, 8 cases of cerebral malaria, 4 cases of cerebral palsy and 2 cases of Guillain Barre`s syndrome.

Table 6: Distribution of cases in control group.

Diagnosis	No. of cases	Percentage
Simple febrile convulsion	27	71.05
Idiopathic epilepsy	11	28.95

Evidence for the diagnosis of TBM observed in our study- history of contact with the patients of active tuberculosis in 28.12% cases; positive tuberculin test in 62.5% cases; associated pulmonary tuberculosis (by x-ray chest) in 78.12% and tuberculous lymphadenitis (by biopsy) in 3.12 % cases and positive smear for AFB in CSF on Z.N. staining in 3.12 % cases. No culture for M. tuberculosis were positive (Table 7).

Table 7: Evidence for the diagnosis of TBM.

Evidence	+ve	-ve	% of +ve cases
H/O contact with patients of active pulmonary TB	09	23	28.12
Tuberculin test	20	12	62.50
Associated tuberculous focus			
Pulmonary (X-ray test)	25	07	78.12
Lymphadenitis (Biopsy)	01	31	03.12
CNS			
Z. N. Stain	01	31	03.12
Culture for AFB	--	--	--

Table 8: Immunization status of TBM patients.

BCG vaccination	No. of cases	Percentage
Vaccinated	07	21.88
Non-Vaccinated	25	78.12

Table 9: Tests for diagnosis of acute bacterial meningitis.

Test	Cases	+ve	-ve	% of +ve cases
CSF Gram`s stain	19	04	15	21.05
CSF culture	19	01	18	05.26

Table 10: CSF-ADA levels (IU/L) in patients of different C.N.S. disorders.

Diseases	No. of cases	Mean±S.D
Tubercular meningitis	32	10.10±2.28
Acute bacterial meningitis	19	03.20± 1.00
Aseptic meningitis	10	02.03± 0.26
Encephalitis	16	1.06±0.25
Brain neoplasm	02	04.43± 2.81
Acute infantile hemiplegia	07	00.84± 0.19
Neurodegenerative disorders	03	00.85±0.25
Enteric encephalopathy	05	00.98±0.25
Acute cerebelletis	04	00.96±0.28
Cerebral malaria	08	00.87±0.26
Cerebral palsy	04	00.85±0.12
Guillian Barre` syndrome	02	01.19±0.33

The highest value was noted in tuberculous meningitis (Table 10).

Table 11: CSF-ADA levels (IU/L) in control group.

Diagnosis	No. of cases	Mean±SD
Simple ferile convulsion	27	0.7362±0.1716
Idiopathic epilepsy	11	0.7354±0.1112

Table 12: CSF-ADA level in TBM according to CSF protein.

Protein (mg%)	Group	No. of cases	CSF –ADA level (IU/L) (mean±SD)
50-100	A	16	08.86±1.19
101-200	B	12	10.36±1.94
>200	C	04	14.27±1.18

One way ANNOVA shows - there significant difference of CSF-ADA level in between 3 groups ($F = 20.609$, $p< 0.001$).

Table 13: CSF-ADA level in TBM according to CSF sugar.

Sugar (mg%)	Group	No. of cases	CSF-ADA level (IU/L) (mean±SD)
≤40	A	21	10.03±2.09
≥40	B	11	10.24±2.68

Students` t test shows the mean difference in CSF-ADA level between these 2 groups is not statistically significant ($p = 0.80$).

Table 14: CSF-ADA level in TBM according to CSF cell count.

Cell counts	Group	No. of cases	CSF-ADA level (IU/L) (mean±SD)
0-100	A	14	08.49±1.41
101-200	B	12	10.12±0.93
>200	C	06	13.80±1.16

One way ANNOVA shows- there significant difference of CSF-ADA level in between 3 groups. ($F = 40.803$, $p< 0.0001$).

DISCUSSION

Tuberculous meningitis still remains an important cause of morbidity and mortality in India due to the lack of early diagnosis of TBM. Tuberculous meningitis continues to confront clinicians with diagnostic problems. Acid fast bacilii may be difficult to find in the CSF on Ziehl Neelsen staining, while culture of mycobacterium tuberculosis from CSF may take 6 to 12 weeks. Even when it is not fatal, irreversible brain damage may results from waiting some weeks for culture proving the diagnosis. In areas with a high prevalence of tuberculosis like India, there need for an alternate highly sensitive test for the early diagnosis of TBM which at the same time approaches the specificity of golden standard.

Adinosine deaminase (ADA) has been reported to be one such test in the diagnosis of tuberculous serositis and meningitis. A sensitivity and specificity of more than 90% has been reported by several workers using the same test.[8,6] It is in this context CSF-ADA was undertaken in the patients of different CNS disorders including different types of meningitis.

The present study is aimed to determine the CSF-ADA levels in different CNS disorders, to compare the CSF-ADA activity in different types of meningitis, to find out the sensitivity and specificity of CSF-ADA in the diagnosis of TBM and to establish the prognostic value of CSF-ADA in TBM.

The present study was carried out in the 112 cases of different CNS disorders, age ranging from 4 months to 12 years with a mean age of 4.12 years and 38 cases (27+11) of control group (simple febrile convulsion and idiopathic epilepsy). The youngest case was of 7 months and the eldest case of 12 years. Out of 112 cases 32 were of TBM, 19 patients of acute bacterial meningitis, and 10 of aseptic meningitis: other groups (other than meningitis) comprised of 51 patients.

Mean age of case group of the present study is similar to Malan et al (1984) though our sample size is less and the control group is mean age is 2.99 years in our study whereas it is 1.58 years in Malan et al.[31] The mean age of TBM patient is 2.4 years with the youngest of 7 months and the eldest is 8 years. 15 cases (46.88%) were between 7 months to 1 years of age and 28 (87.5%) are in first 5 years. this finding was similar to the study of Molavi A et al.[10] Male predominance is observed in both case and control of our study. Male to female ratio in TBM cases was 1.29:1 in present study which is comparable with the study of Udani and Parekh et al where male to female ratio in CNS tuberculosis was 1.27:1.[32]

In the present study, H/O contact with the patient of active tuberculosis was found in 9 cases (28.12%), which is comparable with the study of Abdholgader et al, Alarcon F et al and Udani PM, where they found it 20-30% cases, 32.1% cases and 25.3% cases respectively. Positive tuberculin test was found in 62.5% cases of our study which is almost similar to the finding of Ribera et al.[4,10,33,34] 67% of negative tuberculin test of this study is similar to the finding of Lincoln et al and in contrast with Udani M.[35,36] Evidence of pulmonary TB, hilar lymphadenopathy and consolidation were found in 25 cases (78.12%) of TBM patients in similarity with the findings of Lincoin et al and Zaarbi et al.[35,37]

CSF smear for AFB was positive in 1 case (3.12%) of our study and 2.2 % in Udani PM but Udani PM got positive

culture in 5.15% cases in Lowenstein medium but we did not find any.[38] In most reported cases the frequency with which AFB seen on smear varies between 10% to 90% of cases and CSF culture were positive in 45-90% of cases Haas FJ et al, Selvakumar et al and Prasad et al from India reported positive culture for AFB in 29.5% and 20.6% case of TBM respectively.[6,8,10] Ribera et al in 19874 reported positive AFB culture in 76% of the cases, while Zeihl Nelson stain was found to be positive in only 10% of their cases studied. In this study out of 32 patients of TBM, 7 (21.88%) were vaccinated with BCG and 78.12 % were not. Findings are similar with Alarcon F et al.[33]

Mean CSF-ADA levels in the control group of this study was 0.74±0.16 IU/L. these values are in close proximity with those obtained by Piras et al, Prasad et al and Selvakumar, where their values were 0.64±0.47, 0.70± 0.25,0.67±0.57 and 0.80±0.50 IU/L respectively.[6,8,12]

Mean CSF-ADA level in encephalitis of the present study was 1.06±0.25 IU/L which is significantly raised as compared to control group ($p<0.05$). High values were also met with by Kluge et al during acute inflammatory cerebropathy.[15] Malan et al had carried out CSF -ADA level in one patient of post-measles encephalitis with the ADA level 1.1 and 4.5 IU/L respectively.[31]

In the present study mean CSF-ADA level in brain neoplasm was 4.43±2.81 IU/L. though it is apparently raised from the value of control group but it is not statistically significant($p>0.05$) may be due to small size of sample (only 2 cases). CSF-ADA mean value in brain neoplasm of Piras et al and Ribera et al was 0.85±0.74 and 2.4±1.8 IU/L respectively and number of cases were 6 and 28 respectively.[4,12]

Mean CSF-ADA value in the neurodegenerative disorders and acute infantile hemiplegia in the present study was not significantly raised as compared to the control group ($p> 0.05$). Similar observations were found by Piras et al.[12] In the present study mean CSF –ADA level of acute cerebellitis, cerebral malaria, Cerebral palsy and Gullain Barre` Syndrome is not significantly raised than the control group.

Mean CSF-ADA level in enteric encephalopathy in our study is not significantly raised as compared to the control as found by Piras et al.[12] They found increased serum serum ADA level but CSF-ADA is not increased. So they concluded that increased ADA level does not pass the haemato-encephalic barrier.

In the present study CSF-ADA level was statistically significantly increased in all types of meningitis ($p<0.05$). The rise is maximum in cases of TBM. Mean value is in similarity with Piras et al and Chandra et al. The lower and higher ADA value is observed by Prasad et al and Ribera et al may be due to difference in racial factors and different estimation techniques. CSF-ADA level of encephalitis in this study was significantly higher than control ($p< 0.05$) but when compared with TBM values are values are higher in TBM than encephalitis.

In the present study, in none of the 32 cases of TBM, CSF -ADA level was less than 5IU/L, while in one case of acute bacterial meningitis and in one case of brain tumor it was 6.14 IU/L and 6.42 IU/L respectively. On the basis of these results the sensitivity of CSF-ADA for the diagnosis of TBM at cut-off value of 5IU/L was 100% and specificity was 97.5%.

Ribera et al had studied in all adults patients that may be the possibility of higher cut-off point (9 IUU/L) of ADA level in the diagnosis of TBM.[4,12] In the follow up cases of Piras et al, out of 5 TBM cases 4 (80%) showed progressive decrease of ADA, paralleled by improvement of clinical symptoms and CSF cellular and Biochemical data. Whereas in the present study out of 16 cases 14 (87.5%) showed significant decrease in ADA along with the clinical improvement. In their study 1 (20%) patient died after 1 month due to complications without showing any significant fall of ADA. Whereas in our study 2 cases (12.5%) had shown the same trend.

Ribera et al had found significant lowering of ADA activity between 10-20 days of therapy ($p<0.05$) which is comparable with our findings. Complication is 6.25% in Ribera et al.[4] In these complicated patients we did not find increased level from initial level which is observed by Ribera et al.[4] He explained that initial rise in ADA during the first 10 days of ATT due to;

- The amount of time needed by tubercular antigens
- A greater stimulation of T cell by the release of antigen as a result of the bactericidal effect of chemotherapy.

They observed after this initial phase there is a progressive fall in ADA activity, until it normalizes about 3-4 months later. This gradual fall may be due to the continues elimination of mycobacterial antigen allowing T lymphocytes to regain their quiescent state.

Ribera et al did not find CSF-ADA level below 9IU/L at any time before 4th week of therapy.[4] According to this, the sensitivity of ADA test remained 1 up to this time. On the contrary, in the present study we did not find ADA level below 5 IU/L in any cases during 3-4th week of therapy. According to this, the sensitivity of ADA test remained 1 up to 3-4 weeks of therapy.

When CSF-ADA level in TBM was compared with CSF protein in this study, it was found that with increase in protein level the mean ADA level also increased significantly. Similar findings were observed by Prasad et al8. In the present study when CSF-ADA level in TBM was compared with CSF sugar there was no significant difference ($p<0.05$) in mean CSF-ADA level to CSF

sugar level, similar findings were observed by Prasad et al8.

When CSF-ADA level in TBM was compared with the CSF cell counts, it was found that with increase in cell count the mean ADA level also increased. In our study where pleocytosis occurs in CSF, there were lymphocytic predominance. So this present observation can be comparable with study Prasad et al where they observed increase mean ADA level in relation to increase lymphocyte percentage in CSF.[8]

CONCLUSION

In the present study, a total number of 112 cases of different central nervous system (CNS) disorders and 38 controls (simple febrile convulsion and idiopathic epilepsy) were studied at Government Medical College and Hospital, Aurangabad. Conclusion drawn from the present study were as follows: Male to female ratio in patients of different CNS disorders were 1.38:1, suggesting apparent male predominance. Tuberculous meningitis was common in non-BCG vaccinated (78.12 %) children. Mean CSF-ADA levels (IU/L) were in TBM -10.10±2.28, in acute bacterial meningitis- 3.20±1.00, in aseptic meningitis 2.03±0.23, in encephalitis 1.06±0.25 in brain neoplasm 4.43±2.81 in acute infantile hemiplegia 0.84± 0.19, in neurodgeretive disorders 0.85±0.25, in acute cerebellaritis 0.96±0.28, in enteric encephalopathy 0.98±0.25, in cerebral malaria 0.87±0.26, in cerebral palsy 0.85±0.12 and in Gullian Barre` syndrome 1.19±0.38. The highest value was noted in TBM. In the control group mean CSF-ADA level was 0.74±0.16 IU/L with the range 0.42-1.28 IU/L. Statistically significant higher values than control group were obtained in the CSF in each of the three meningitis groups and as well as in encephalitis group ($p<0.05$); while in other group, CSf-ADA did not differ significantly from that of control group ($p<0.05$). CSF-ADA level is statistically significantly higher in TBM than acute bacterial meningitis, aseptic meningitis and encephalitis ($p<0.05$).

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