Original Research Article

Clinical study of meningitis in children and role of adenosine deaminase in differentiating tubercular from non-tubercular meningitis

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Received: 08 May 2019

Revised: 31 May 2019

Accepted: 10 June 2019

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ABSTRACT

Background: In diseases where cell mediated immunity plays an important role like in tuberculosis, CSF (Cerebrospinal fluid) adenosine deaminase (ADA) activity is increased. Hence, this testing is done especially among children with suspected tubercular meningitis. The objective of this was to study role of Adenosine Deaminase in differentiating tubercular from non-tubercular meningitis.

Methods: This was a hospital based cross sectional study was carried out among 50 children of proven meningitis for a period of two years. CSF ADA levels were done for all cases. They were divided into tubercular meningitis and non-tubercular meningitis group and compared.

Results: Incidence of tuberculous meningitis (TBM) was found high in the age group 5-8 years. Male:female ratio was 2.3:1. Fever was present in all cases followed by vomiting and neck rigidity. CSF AFB was positive in 3 cases (6%). Neuroimaging was done in all cases in which 3 patients had basal exudate in which 2 patients had TBM and 1 patient was Non-TBM. 3 patients had hydrocephalus in MRI in which 2 had TBM diagnosed and 1 had non-TBM. As per ADA levels, 10 were diagnosed as TBM out of which 8 patients had ADA level ≥ 10 IU/L and 2 had ADA level < 10 IU/L which was missed by ADA and later confirmed by other modalities.

Conclusions: It was concluded that if ADA level in CSF is ≥ 10 IU/L the diagnosis of TBM should be considered.

Keywords: ADA levels, CSF, Diagnosis, Neck rigidity, Neuroimaging, Tubercular meningitis

INTRODUCTION

Developing countries host tuberculosis (TB) as the most prominent public health problem. Children are affected the worst. World Health Organization states that active tubercular disease has affected 16 million people. Globally 8.5 million people develop active TB every year. Around two million die every year due to TB.¹ Tuberculous meningitis (TBM) affects mainly the people from lower social classes in both the developed as well as developing countries.²

It has been estimated that every year about five lakh people die because of TB. Childhood TB represents about 8.3% of the total cases in India.³ HIV-AIDS has increased the seriousness of TB problem added with increasing incidence of multi drug resistant TB.⁴

Tuberculous meningitis (TBM) is among the all types of extra pulmonary TB one of the most serious problems. The incidence of TBM has been estimated at 7 to 12 percentage among all new cases of TB. These estimates are applicable to the developing countries. TBM must be

attended quickly other delay can lead to poor outcome. Overall the poor outcome has been estimated at 20 to 25 percentage of all the cases.⁵

TBM presents with nonspecific clinical features and due to such overlapping features, diagnosis is a challenge. It mimics viral meningitis as well as pyogenic meningitis.⁶ Due to conflict over appropriate diagnostic test for TBM, the treatment is delayed.⁷ There is lack of sensitivity of available tests used for diagnosis of TBM.⁸ Certain tests with good sensitivity and specificity are not affordable for most of the populations.⁹ Hence, there is a need for a diagnostic test which is affordable, easily available.

TBM diagnosis is dependent on CSF culture. But culture takes a long time to give results, not available everywhere, costly. CSF cytology findings are not specific as they vary from patient to patient. same is the case with CSF biochemistry.¹⁰

Adenosine deaminase (ADA) is an enzyme that catalyses the deamination of adenosine, forming inosine in the process.¹¹ The chief physiological function of ADA is related to lymphocytic proliferation and differentiation.¹² As a marker of cellular immunity, activity is found to be elevated in those diseases in which there is a cell-mediated immune response.¹³

The present study was conducted to confirm the usefulness of adenosine deaminase assay for diagnosis of tuberculous meningitis.

METHODS

The present study was conducted in the Department of Paediatric and child health unit in Tertiary health care centre in Dhule, from December 2015 to October 2017. The study design was hospital based cross sectional study. A total of 50 paediatric patients with meningitis admitted to Paediatric ICU were selected for the study.

Inclusion criteria

- Patient presenting with clinical signs and symptoms of meningitis
- CSF Picture suggestive of meningitis.

Exclusion criteria

- Patient with febrile convulsion with normal CSF finding
- Patient with focal convulsion with normal CSF finding
- Patient having non-infectious meningitis
- Meningitis with contaminant illness such as HIV/ immunosuppressive therapy
- Condition which can contribute in elevation of CSF-ADA activity in body fluids like- typhoid fever, infectious mononucleosis, viral fever, rheumatologic

disease, intra-cranial tumor and lymph-proliferative disorder.

- Traumatic CSF.

Method of collection of data

Meningitis among the children was diagnosed based on symptoms, signs and analysis of CSF. Meningitis was classified as tubercular and non-tubercular. 10 children with TBM and 40 children with non TBM were studied and compared for different parameters.

Group 1: TBM Group

This group of children consisted of those who had history of close contact with TB case, clinically suspected TB, radiologically suspected TB, a positive Mantoux test, and CSF picture giving indications for TBM as well as AFB seen on culture of CSF or ZN staining.

Group 2: Non TBM Group

- Pyogenic meningitis (PM): This group of children consisted of those whose gram staining of CSF was positive for bacteria as well as picture of CSF suggestive of PM.
- Partially treated meningitis (PPM): This group of children consisted of those who received antibiotic treatment before CSF analysis.
- Viral meningitis (VM): This group of children consisted of those with pleocytosis in CSF of less than 100/mm³, also they had lymphocytosis, and increased sugar levels.

The data was analysed using proportions, mean values. Students t test, chi square test was applied wherever appropriate.

RESULTS

Table 1 shows comparison of clinical examination findings in two groups. Fever, headache, loss of consciousness and convulsions were similar in both the groups but vomiting and neck rigidity was more common in TBM group compared to the non TBM group. Most common was fever in both the groups in all cases. This was followed by vomiting was more common in TBM group compared to non TBM group. Headache was seen in half of the cases in both the groups. Neck rigidity was more common in TBM group compared to non TBM group. Loss of consciousness was seen in half of the cases in both the groups.

Table 2 shows comparison of CSF Laboratory parameters, CSF ADA levels, and Mantoux test in two groups. It was found that the mean values of total count were significantly more in non TBM group compared to the TBM group. But lymphocyte and protein mean values were significantly more in TBM group compared to non TBM group. The CSF ADA levels were significantly

increased in the TBM group (16.82 ± 6.43) compared to the non TBM group (5.68 ± 2.54). It is clear that Mantoux

positivity was 30% in the TBM group compared to zero percentage in the non TBM group.

Table 1: Comparison of clinical examination findings in two groups.

Clinical examination	TBM group, (n=10)	Non TBM, (n=40)	Total
Fever	10 (100%)	40 (100%)	50 (100%)
Vomiting	9 (90%)	24 (60%)	33 (66%)
Headache	5 (50%)	19 (47.5%)	24 (48%)
Neck rigidity	8 (80%)	25 (62.5%)	33 (66%)
Loss of consciousness	5 (50%)	18 (45%)	23 (46%)
Convulsion	4 (40%)	18 (45%)	22 (44%)

Table 2: Comparison of CSF Laboratory parameters, CSF ADA levels, and Mantoux test in two groups.

Parameters		TBM group, (n=10)	Non TBM, (n=40)	P value
CSF Laboratory parameters	Total count	201.8 $\pm$ 89.78	476.1 $\pm$ 577.24	<0.0001
	Neutrophil	3.6 $\pm$ 3.50	49.87 $\pm$ 34.40	<0.0001
	Lymphocyte	95.8 $\pm$ 5.20	49.97 $\pm$ 34.55	<0.0001
	Sugar	34.2 $\pm$ 11.75	41.4 $\pm$ 10.46	0.0633
	Protein	329.7 $\pm$ 121.82	126.5 $\pm$ 62.87	<0.0001
CSF ADS levels		TBM group, (n=10)	Non TBM, (n=40)	Total
P <0.0001	0-5	0	22 (55%)	22 (44%)
	6-10	3 (30%)	16 (40%)	19 (38%)
	11-15	1 (10%)	2 (05%)	03 (06%)
	>15	6 (60%)	0	06 (18%)
	ADA Level (IU/L)	16.82 $\pm$ 6.43	5.68 $\pm$ 2.54	50
Mantoux Test	Positive	3 (30%)	0	03 (06%)
	Negative	7 (70%)	40 (100%)	47 (94%)

Table 3: Comparison of ZN-AFB test, neuro-imaging results and GeneXpert results in the two groups.

Parameters		TBM group, (n=10)	Non TBM, (n=40)	Total
ZN AFB Staining	Positive	3 (30%)	0	3 (6%)
	Negative	7 (70%)	40 (100%)	47 (94%)
Neuroimaging	Normal	6 (60%)	38 (95%)	44 (88%)
	Basal Exudate	2 (20%)	1 (2.5%)	3 (06%)
	Hydrocephalus	2 (20%)	1 (2.5%)	3 (06%)
Gene Xpert	Positive	8 (80%)	0	8 (16%)
	Negative	2 (20%)	9 (22.5%)	11 (22%)
	Not Done	0	31 (77.5%)	31 (62%)

Table 3 shows comparison of ZN-AFB test, neuro-imaging results and GeneXpert results in the two groups. Similar to the Mantoux test, ZN AFB staining was also found to be positive in 30% of TBM group compared to zero percentage in the non TBM group. It was found that 2 (20%) cases of Basal Exudate and 2 (20%) cases of Hydrocephalus were seen in TBM Group, which was higher in comparison to non TBM group. GeneXpert positivity was 80% in the TBM group compared to non TBM group. This shows that GeneXpert is 100% specific

test. Table 4 shows comparison of culture test results in the two groups. It was found that 30 (60%) cases have no growth within 48 hrs while, 20 (40%) cases have found bacterial growth where *S. pneumonia* in 8 cases, *N. meningitides* in 5 cases. *Klebsiella pneumoniae* in 4 cases and *Pseudomonas aeruginosa* in 3 cases were from Non TBM group. The definitive culture for TB is LJ media culture that is solid culture media or liquid culture middle brook agar based both cultures are not available at our hospital, so we are not able to send it.

Table 4: Comparison of culture test results in the two groups

Culture	TBM group, (n=10)	Non TBM, (n=40)	Total
No growth	10 (100%)	20 (50%)	30 (60%)
Bacterial growth	0	20 (50%)	20 (40%)
<i>S. pneumonia</i>		8	
<i>N. meningitides</i>		5	
<i>Klebsiella pneumoniae</i>		4	
<i>Pseudomonas aeruginosa</i>		3	

Table 5 shows clinical and lab diagnosis of suspected TBM and non TBM. It was found that TBM meningitis in 10 (20%) cases, while Non TBM meningitis 40 (80%) cases divided such as, higher of Pyogenic meningitis 21 (42%), Partial meningitis 09 (18%), Viral meningitis 10 (20%) cases.

Table 6 shows sensitivity and specificity of CSF ADA level. From the above table, by using cut off level of ADA level <10 IU/L TBM group with Non TBM group had sensitivity 80.00%, specificity 92.50%, Positive Prediction Value 72.73% and Negative Prediction Value 94.87% with statistically significant.

Table 5: Clinical and lab diagnosis of suspected TBM and non TBM.

Etiology	Total
TBM meningitis	10 (20%)
Non TBM meningitis	40 (80%)
• Pyogenic meningitis	21 (42%)
• Partial treated meningitis	09 (18%)
• Viral meningitis	10 (20%)
Total	50 (100%)

Table 6: Sensitivity and specificity of CSF ADA level.

CSF ADA Level	TBM group, (n=10)	Non TBM, (n=40)	Total
<10 IU/L	2 (6.66%)	37 (85%)	39 (78%)
>10 IU/L	8 (93.3%)	3 (15%)	11 (22%)
Sensitivity	80.00%		
Specificity	92.50%		
PPV	72.73%		
NPV	94.87%		
P Value	< 0.0001		

Table 7: Comparison of sensitivity and specificity of CSF ADA levels with other diagnostic modalities.

Etiology	Mantoux test	ZN-AFB	Neuroimaging	Gene Xpert	CSF ADA Level
Sensitivity	30%	33.33%	40%	80%	80.00%
Specificity	100%	100%	95%	100%	92.50%
PPV	100%	100%	66.67%	100%	72.73%
NPV	85.11%	60%	86.36%	95.24%	94.87%

Table 7 shows comparison of sensitivity and specificity of CSF ADA levels with other diagnostic modalities.

From the above table, by using different diagnostic method, it was found that of CSF ADA Level and Gene Xpert were highly sensitive (80.00% each) compared to different methods such as Mantoux Test, ZN-AFB, and Neuroimaging. Specificity of Mantoux, ZN-AFB,

GeneXpert was 100% but that of CSF ADA levels was lesser i.e. 92.5%.

DISCUSSION

In the present study, the symptoms of paediatric patients were fever in all 50 (100%). While other symptoms such as vomiting and Neck rigidity were in (66%) patients in

each, headache was in (48%), Loss of consciousness (46%), convulsion (44%) patients. These findings are similar with study by Malla K et al, who found fever in 100% followed by Neck rigidity 90% and Bindu TH et al, who reported fever in 96.8% followed by seizure 93.7%.^{14,15}

The CSF total count (201.8±89.78), Neutrophils (3.6±3.50) were low and Lymphocyte (95.8±5.20) and Protein (329.7±121.82) highest with TBM group compared with non TBM group and was significant. (P<0.0001). Similar findings were noted by other study Malla K et al.¹⁴ TBM is a chronic disease, and, hence, the CSF usually appears clear and has moderate numbers of leukocytes, with the predominance of lymphocytes.

In the present study, ADA Level was 16.82±6.43 with TBM group was more than non TBM group i.e. 5.68±2.54 and statistically significant (P<0.0001). Similar findings were reported by Gupta BK et al¹⁶ and Bindu TH et al.¹⁵ These results showed that ADA secretion by T-lymphocytes in response to mycobacterial antigen vary and lower activity is observed in CSF of paediatric TBM patients.

By Neuroimaging examination, it was found that 2 (20%) cases of Basal Exudates and 2 (20%) cases of Hydrocephalus were seen in TBM Group, which was higher in compare to non TBM group such as that 1 (2.5%) case of Basal Exudates and 1 (2.5%) cases of Hydrocephalus. Similar findings were given by Bindu TH et al, where they found that Hydrocephalus was present in 59.37% of the cases and Basal Exudates in 25% of the cases.¹⁵ Similar results were reported by Gupta BK et al, who found it as 10.53%.¹⁶

In the present study, 30 (60%) cases have no growth within 48 hrs. while, 20 (40%) cases have found bacterial growth where *S. pneumonia* in 8 cases, *N. meningitides* in 5 cases. *Klebsiella pneumoniae* in 4 cases and *Pseudomonas aeruginosa* in 3 cases were from Non TBM group. Similar findings were given by Qamar FN et al.¹⁷

Gene Xpert examination was positive in 80% of the cases from TBM group and none from non TBM group. Similar findings were reported by NQ Nhu et al.¹⁸

By using cut off level of ADA level <10 IU/L TBM group with Non TBM group had sensitivity 93.33%, specificity 85%, Positive Prediction Value 90.32% and Negative Prediction Value 89.47% with statistically significant. Gupta BK et al, reported that sensitivity was 94.73% and the specificity was 90.47%.¹⁶ They concluded that ADA estimation in CSF is not only simple, inexpensive and rapid but also fairly specific method for making a diagnosis of Tuberculous etiology in children with meningitis. In addition, it was found that of CSF ADA Level was highly sensitive 80.00% compare to different clinical method such as Gene Xpert, Mantoux

Test, ZN-AFB, and Neuroimaging were have (80%, 30%, 33.33%, 40%) respectively.

CONCLUSION

Diagnosis of meningitis is primarily done by clinical signs, symptoms and CSF study, however in many patients it becomes difficult to differentiate between Tuberculous and non-Tuberculous meningitis. ADA estimation in CSF is rapid and affordable adjunct in differentiating TBM from non-TBM. ADA estimation in CSF is simple and rapid but also fairly specific method for making a diagnosis of tuberculous etiology in children with meningitis. It is concluded that if ADA level in CSF is ≥10IU/l the diagnosis of TBM should be considered.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Yadav A, Pandey D. Clinical study of meningitis in children and role of adenosine deaminase in differentiating tubercular from non-tubercular meningitis. *Int J Contemp Pediatr* 2019;6:1695-700.