Indian Journal of Clinical Biochemistry, 2008 / 23 (3) 299-301

BRIEF COMMUNICATION

ADENOSINE DEAMINASE AND C-REACTIVE PROTEIN IN CEREBROSPINAL FLUID FOR DIFFERENTIAL DIAGNOSIS OF TUBERCULAR MENINGITIS IN CHILDREN

Shrish Bhatnagar, Farzana K Beig*, Ashraf Malik*

Department of Pediatric Gastroenterology, SGPGIMS, Lucknow.
**Department of Pediatrics, Jawahar Lal Nehru Medical College, Aligarh Muslim University, Aligarh.*

ABSTRACT

Adenosine deaminase and C-reactive protein in CSF were assessed in 72 cases of Tubercular meningitis, 24 cases of partially treated pyogenic meningitis, 20 cases of Aseptic meningitis and 8 cases of febrile seizures. Mean Adenosine deaminase value was 12.12±3.13 IU/L for Tubercular meningitis group. It was significantly higher (p<0.001) as compared to partially treated pyogenic meningitis (5.39±2.70 IU/L) and aseptic meningitis (1.92±0.56 IU/L) groups. A combination of clinical criteria along with biochemical test of Adenosine deaminase and C-reactive protein in CSF increased the sensitivity of diagnosing Tubercular meningitis and differentiating it from other forms of meningitis at an early stage.

KEY WORDS

Adenosine deaminase and C-reactive protein in CSF, Tubercular meningitis, Children

INTRODUCTION

Tubercular meningitis (TBM) continues to be an important cause of hospital admission, death, and neurological disability in children in India. The illness accounts for 1-4 % of total pediatric hospital admission in different part of the country (1). Early diagnosis and adequate management is the key to decrease mortality and disability. Partially treated pyogenic meningitis, a condition which nowadays is quiet a rampant problem because of irrational use of antibiotics mimics TBM both clinically as well as in the cerebrospinal fluid (CSF) analysis and thus for a clinician differentiating TBM from partially treated pyogenic meningitis becomes quiet difficult on the routine diagnostic test available (2).

Address for Correspondence :

Dr. Shrish Bhatnagar,
Department of Pediatric Gastroenterology
Sanjay Gandhi Post Graduate Institute of
Medical Sciences, Lucknow. U.P. - 226017.
Ph: 09358208555
E-mail: drshrishbhatnagar@gmail.com

MATERIALS AND METHODS

The study was conducted at the Department of Pediatrics, Jawahar Lal Nehru Medical College & Hospital in collaboration with the Department of Biochemistry, Faculty of Life Sciences, AMU, Aligarh for a period of one year from November 2003 to November 2004. 124 patients of meningoencephalitis, between 1month to 12 years of age were included in the study and were divided in 4 groups:-

Group A - TBM (n=72) : Diagnosis was established on the basis of clinical picture, CSF biochemistry, CSF culture, CT scan findings and response to therapy.

Group B - Partially treated pyogenic meningitis (n=24) : It was diagnosed on the basis of acute onset of symptoms and history of receiving antibiotics (entral/parentral), CSF pleocytosis and with high protein and low CSF sugar, positive CSF/Blood culture and CT Scan findings.

Group C - Aseptic meningitis (n=20) : It was diagnosed with predominance of lymphocytic pleocytosis, normal to moderately raised CSF protein, normal to low CSF sugar and negative bacterial, mycobacterial, fungal culture.

Group D - Febrile seizures (n=8) : Patients having typical history with normal CSF counts and biochemistry and negative CSF culture.

Clinical criteria by Kumar et al (Fever =>7 days; Optic atrophy;

Table 1: Comparison of CSF Biochemistry in TBM and other groups

Group	Total no of cases	Cell Count ($x 10^3/mm^3$)	Protien (mg%)	Sugar (mg%)	ADA (IU/L)	CRP Positive No. (%)
A	72	28.0 ± 10.9	112.0 ± 18.1[#]	51.0 ± 3.0[#]	12.12 ± 3.13[*]	0[*]
B	24	238.0 ± 43.8[#]	137.0 ± 12.5[#]	57.0 ± 2.4[#]	5.39 ± 2.70[*]	20(83.33%)[*]
C	20	37.0 ± 1.7	37.0 ± 1.9	70.0 ± 2.4	1.92 ± 0.56[*]	2(10%)[*]
D	8	<5	24.0 ± 1.2	71.0 ± 2.0	2.04 ± 0.72[*]	0[*]

[#]p value A vs. B Non-significant; [*] p value A vs. B; A vs. C; A vs. D <0.001 (significant)

Focal deficit; Extra pyramidal symptoms; polymorph >20 cells; CSF leucocytes <50%) was used in this study (3). Presence of 3 or more criteria was considered consistent with the diagnosis of TBM.

Adenosine deaminase (ADA) estimation : The sensitive colorimetric method of Galanti and Giusti (4) was used in this study with some minor modifications. The activity of ADA was measured in a cell free CSF sample (either fresh or stored for a less than seven days at -20°C). Optical density was measured at 628nm using CINTRA 5 spectrophotometer (Beckman, U.S.A.). Enzyme activity was expressed in IU/L (37°C). Control specimens of known value were included in each run. A value of > 8 IU/L was considered consistent with the diagnosis of TBM, chosen on the basis of various studies conducted previously (6, 9, 11).

C - reactive protein (CRP) Estimation : Span Diagnostic reagent kit, Surat [code 25934] used for in vitro detection of C - reactive protein (CRP) in human sera and body fluids by qualitative and semi quantitative rapid latex slide test was used in this study. All the study patients were followed up to 6 months and all the above details were recorded systematically and extensively on pre formed Performa.

Statistical analysis : Various data was collected, organized and statistically analyzed for significance (p value), using unpaired t-test and Chi square test. Sensitivity, specificity, positive predictive value and negative predictive values of various diagnostic modalities used were calculated. Where there was a wide range of variation in parameters, the geometric mean was used and the standard deviation was derived out using this mean.

RESULTS

The comparisons of various CSF laboratory tests between the various groups are given in Table 1. The diagnostic yield of combined clinico-biochemical criteria is depicted in Table 2. It is evident from the table that the criterion was more helpful in differentiating TBM at early stages than the advanced stages. CT scan of the TBM patients showed hydrocephalus (82%) as most common finding followed by basal exudates (76%), infarcts (14%) and tuberculoma (7%). It was normal in 2.2% (n=3) of the patients.

DISCUSSION

As evident from the data in the present study clinical criteria alone or routine CSF cytological /biochemical tests are not reliable in differentiating TBM from other forms of meningitis. ADA is an enzyme with principal biologic activity in T – lymphocytes (10). Raised levels have been used as diagnostic marker in many studies (5-9, 11). Similarly CSF-CRP by latex agglutination is a useful test for bacterial meningitis with reported high sensitivity(12,13,14).The mean ADA value in our study was 12.12±3.13 IU/L for TBM group and was significantly higher (p<0.001) than the partially treated pyogenic meningitis (5.39±2.70 IU/L) and aseptic meningitis (1.92±0.56 IU/L).

Table 2: Statistical Indices in relation to Diagnostic Modalities for TBM Stage I, II & III

	Sensitivity			Specificity		
CRITERIA	I	II	III	I	II	III
Clinical	37.03%	51.85%	81.71%	58.06%	61.74%	66.15%
Clinical & Positive ADA	67.34%	75.92%	86.11%	73.16%	78.21%	83.13%
Clinical, Positive ADA & Negative CRP	76.54%	83.14%	88.88%	79.55%	80.11%	87.79%

There has been conflicting report regarding the diagnostic value of ADA in children as compared to adults, in whom 96-100% sensitivity has been, described (5, 6, 17). Our study confirms the utility of ADA as diagnostic test for TBM in children. The clinical criteria by Kumar et al(3) when applied in our patients had sensitivity of 37.03%, 58.06% and 81.71% respectively for diagnosis of TBM stage I, II and III. This highlights the low power of the clinical criteria for diagnosis of TBM. This can be attributed to the features incorporated in these criteria, which pertains to the later stages of the disease. These clinical criteria can thus be presumed to be of diagnostic help only for advanced stage Tubercular meningitis. With the use of CSF-ADA, one can pick up early cases of TBM, a conclusion akin to that drawn by Misra et al (12). Studies by Seth et al (15) and Bhargava et al (16) showed similar findings in terms of CT scan findings in TBM patients.

Based on this study results it can be concluded that in the absence of reliable clinical criteria, high yield AFB culture/ smear and poor affordability of CT scan, estimation of CSF ADA and CRP is warranted in all patients for early diagnosis of TBM or where there is a diagnostic dilemma, persisting after the usual line of investigations.

REFERENCES

1. Upadhyay GC, Tripathi BN, Sukla RK, Singh KN. Tuberculous meningitis in children: a clinico-laboratory correlation of CSF findings for early diagnosis. Ind J Paed 1984; 51(413): 633-6.
2. Mishra OP, Loiwal V, Ali Z, Nath G, Chandra L. CSF Adenosine deaminase activity for the diagnosis of tuberculous meningitis in children. J Trop Pead 1996; 42(3):129-32.
3. Kumar R, Singh SN, Kohli N. A diagnostic rule for Tuberculous meningitis. Arch Dis Child 1999; 81(3):221-4.
4. Guisti G, Galanti B. Adenosine deaminase: colorimetric method. In Methods of Enzymatic Analysis. 5th edition. Edited by: Bergmeyer HU. Weinheim (Germany): Verlag Chemie; 1984:315-23.
5. Ribera E, Martinez-Vazquez JM, Ocaña I, Segura RM, Pascual C. Activity of adenosine deaminase in cerebrospinal fluid for the diagnosis and follow-up of Tuberculous meningitis in adults. J Infect Dis 1987;155(4):603-7.
6. Pettersson T, Klockars M, Weber TH, Somer H. Diagnostic value of cerebrospinal fluid adenosine deaminase determination. Scand J Infect Dis 1991; 23(1):97-100.
7. Malan C, Donald PR, Golden M, Taljaard JJ. Adenosine deaminase levels in cerebrospinal fluid in the diagnosis of tuberculous meningitis. J Trop Med Hyg 1984; 87(1):33-40.
8. Piras MA, Gakis C. CSF Adenosine deaminase activity in tuberculous meningitis. Enzyme 1972; 14:311-7.
9. Prasad R, Kumar A, Khanna BK, Mukerji PK, Agarwal SK, Kumar A, Srivastava VM. Adenosine deaminase activity in cerebro-spinal fluid for diagnosis of Tuberculous meningitis. Ind J Tub 1991; 38:99-102.
10. Daddona PE, Kelley WN. Human adenosine deaminase Purification and Subunit structure. J Biol Chem 1977; 252:110-15.
11. Coovadia YM, Dawood A, Ellis ME, Coovadia HM, Daniel TM. Evaluation of adenosine deaminase activity and antibody to Mycobacterium tuberculosis antigen 5 in cerebrospinal fluid and the radioactive bromide partition test for the early diagnosis of tuberculosis meningitis. Arch Dis Child 1986; 61(5): 428–35.
12. Peltola H, Jaakkola M. Serious bacterial infection: C-reactive protein as a serial index of severity. Clin Pead 1988; 27(11): 532-7.
13. John M, Raj IS, Macaden R , Raghuveer TS, Yeswanth M, Meundi DM. Cerebrospinal fluid C-Reactive Protein-a bedside test in rapid diagnosis of bacterial meningitis. J Trop Pead 1990; 36(5):213-7.
14. De Beer FC, Kirsten GG, Gie RP, Beyers N, Strachman AF. Value of C reactive protein measurement in tuberculous, bacterial, and viral meningitis. Arch Dis Child 1984; 59(7):653-6.
15. Seth R, Sharma U. Diagnostic Criteria for Tuberculous meningitis. Ind J Pead 2002; 69(4):299-303.
16. Bhargava S, Gupta AK, Tandon PN. Tuberculous meningitis—a CT study. Br J Radiol 1982; 55: 189-96.
17. Rana SV, Singhal RK, Kartar S, Kumar L. Adenosine deaminase levels in cerebrospinal fluid as a diagnostic test for Tuberculous meningitis in children. Ind J Clin Biochem 2004; 19(2): 5-9.