CEREBROSPINAL FLUID ADENOSINE DEAMINASE ACTIVITY AND C-REACTIVE PROTEIN IN TUBERCULOUS AND PARTIALLY TREATED BACTERIAL MENINGITIS

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ABSTRACT

Adenosine deaminase (ADA) activity measurement and C-reactive protein (C-RP) detection were done in CSF of 27 tuberculous meningitis (TBM) and 8 patients of partially treated bacterial meningitis, apart from routine biochemical tests. Both the groups had comparable CSF cell count, protein and sugar concentrations. The mean CSF ADA activity was significantly raised in TBM as compared to partially treated bacterial meningitis patients ($p < 0.05$). A cut-off ADA level of ≤5 Iμ/L and C-RP positivity were used for differentiation of partially treated bacterial from TBM cases. Based on this, the sensitivity and specificity of ADA and C-RP were 62.5%, 88.9% and 75%, 100%, respectively. Since both the tests are simple and take lesser time to perform, they can be used as rapid diagnostic tests to remove diagnostic dilemma between the two diseases.

Key words: *ADA activity, C-RP, Meningitis.*

A precise etiological diagnosis of meningitis in children is required so that appropriate therapy can be started at the earliest. Most of the cases of bacterial meningitis can be distinguished from tuberculous meningitis (TBM) by conventional cerebro-spinal fluid (CSF) biochemistry and culture studies. However, confusion is caused by partially treated bacterial meningitis cases who present with low cell count in CSF, at times with lymphocytic predominance and negative bacterial culture.

In recent years, an elevated CSF adenosine deaminase (ADA) activity has been shown to be a promising test for the diagnosis of TBM(l-3), but the results were less reliable in children(4,5). Detection of CSF C-reactive protein (C-RP) is another test, which is positive in bacterial meningitis with variable sensitivity(6-9). In view of such observations, the present study was conducted to find out the usefulness of these two tests in differentiating partially treated bacterial meningitis from cases of TBM.

Material and Methods

The present study was conducted on 35 patients, aged 2 months to 12 years, and were divided into two groups.

(i) Tuberculous meningitis

This group included 27 patients; of

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these 4 were confirmed TBM (CSF culture and smear were positive for *Mycobacterium tuberculosis* in 3 and 1 had positive lymph node biopsy) while 23 had clinically suspected TBM (diagnosis based on compatible history, clinical findings, CSF abnormality, positive Tuberculin and/or BCG test, lesion on X-ray chest, CT Scan and response to antitubercular therapy).

(it) *Partially treated bacterial meningitis*

This group had 8 patients who were clinically diagnosed as bacterial meningitis and had received inappropriate antibiotics therapy prior to admission. CSF showed leucocytosis, raised protein, low sugar concentration, was sterile on culture and subjects responded to antibiotics therapy.

ADA assay

The ADA activity in CSF was measured by the method of Giusti(10). CSF samples were kept in deep freezer and assay was done within a week. Optical density was measured spectrophotometrically, using UV-1201 (Shimadzu) spectrophotometer, at 265 nm in an assay mixture (final volume 2 ml) containing 0.025 mM adenosis, 10 mM Tris-HCl (pH 7.4), 0.15 M NaCl, 1.25% glycerol and 0.1 ml CSF. One unit of activity represents for the deamination of one micromole of adenosine per min at 37°C temperature and expressed as IU/L.

C-RP detection

This was done on undiluted CSF samples with the help of qualitative agglutination test using C-RP kit (Span Diagnostics Pvt. Ltd. Surat, India).

Student's 't' and chi-square (λ^2) test were used to analyze the data for statistical significance.

Results

The comparison of various CSF laboratory tests between TBM and partially treated bacterial meningitis are presented in *Table* I. The CSF cell count, protein and sugar concentrations did not differ significantly between the two groups. The ADA activity in CSF was significantly raised in TBM as compared to partially treated bacterial meningitis ($P < 0.05$). The individual distribution of ADA levels in the two group of patients are shown in Fig. 1. By taking decreased ADA activity (cut-off level ≤ 5 IU/L) for differentiation of partially treated bacterial meningitis from TBM patients, the test had sensitivity and specificity of 62.5% and 88.9%, respectively.

C-RP was only positive in CSF of partially treated bacterial meningitis with, sensitivity and specificity of 75% arid 100%, respectively. When C-RP positivity in these patients was compared with TBM cases, the difference was significant ($p < 0.001$).

Discussion

The results of the present study confirm that partially treated bacterial meningitis can not be differentiated reliably from TBM cases on the basis of routine CSF cytology and biochemical tests. CSF culture was sterile in all the patients of the former group. Thus, to differentiate between the two disease conditions, it becomes imperative to apply certain other tests.

Adenosine deaminase is an enzyme, with principal biological activity in T-

TABLE I— *Comparison of Various CSF Parameters Between Tuberculous Meningitis and Partially Treated Bacterial Meningitis [Mean ± SD (range)]*

Groups	No. of cases	Cell count (per mm^3)	Protein (mg/dl)	Sugar (mg/dl)	ADA level (IU/L)	C-RP Positive
Tuberculous meningitis	27	228.6 ±133.8 (95-570)	210.7 ±144.5 (73-650)	37.9 ±18.3 (15-96)	9.4 ±5.4 (4.0-22.5)	0 (0.0%)
Partially treated bacterial meningitis	8	290.0 ±175.9 (140-650)	176.9 ±85.5 (75-300)	33.9 ±15.3 (10-59)	5.2 ±2.2 (2.0-8.0)	6 (75.0%)*
p value		NS	NS	NS	<0.05	

* Number (percentage) given, $\chi^2 = 19.44$, $p < 0.001$.

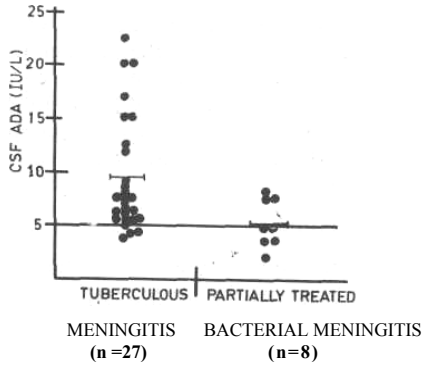

Fig. 1. Individual distribution of CSF ADA levels in TBM and partially treated bacterial meningitis patients.

lymphocytes. It is required for lymphocyte proliferation and differentiation. The enzyme activity is known to be elevated in certain infection where immunity is cell mediated like in CSF of TBM patients(l-3). The source of raised ADA in CSF'of TBM patients may be the damaged blood brain barrier permitting ADA to enter into CSF from the blood or adjacent cerebral tissue and/or as a result of lymphocytic proliferation indicating local immune response(4). In the present study, the mean CSF ADA activity (9.4 TU/L) in TBM cases was significantly elevated as compared to partially treated bacterial meningitis (5.2 IU/L) ($p < 0.05$). Malan et al.(4) also demonstrated the same significant difference level between the two group. However, it appears that complete differentiation between these two diseases is not possible on the basis of CSF ADA activity alone because of overlapping enzymatic levels and lower sensitivity of the test (cut-off level ≤5 IU/L) *(Fig. 1)*.

The detection of C-RP in CSF by latex agglutination method is a useful test for the diagnosis of bacterial meningitis with high sensitivity (91 to 100%)(6,8,9). The mechanism by which C-RP enters in

the CSF could be passive diffusion across the highly inflammed meninges or *de-novo* synthesis in central nervous system(6). In our study, C-RP was detectable in CSF of 6 of 8 (75%) cases of partially treated bacterial meningitis. Negative C-RP in CSF samples of two patients may be related to the nutritional status and severity of infection(8). Benjamin *et al.(7)* have observed still a lower sensitivity (66%) of the test when Laser Nephelometry was used to detect C-RP in CSF of cases of bacterial meningitis. Since it was only positive in partially treated bacterial meningitis, it had a specificity of 100%.

Thus, it is clearly evident that neither CSF ADA level nor C-RP positivity alone could differentiate the two disease conditions completely because of lower sensitivity of the tests. So within the constraint of small sample size, it can be concluded that ADA estimation is more useful in tuberculous meningitis while C-RP estimation is more helpful in culture negative patients of partially treated bacterial meningitis.

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