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Diagnostic Utility of CSF Adenosine Deaminase and C - Reactive Protein Estimation In Meningitis in Adults

KEYWORDS: Tuberculous meningitis, pyogenic meningitis Adenosine Deaminase, C - reactive protein, GALANTI and GIUSTI

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ABSTRACT *Rapid and accurate diagnosis of meningitis is important, because delay in proper treatment can be harmful or even fatal. Combined use of the rapid screening tests like C Reactive Protein level and Adenosine Deaminase activity could be of much help in the differentiation of various types of meningitis in adults. A total of 50 samples of CSF and Serum were collected from Patients attending in-patient departments of Tirunelveli medical college hospital with meningitis were taken for study.CSF ADA was estimated in all patients by colorimetric method of GALANTI and GIUSTI and C Reactive Protein in CSF was estimated based on latex agglutination. Out of 50 cases, 46% cases were Tuberculous Meningitis, 10% was of Pyogenic Meningitis and 44% was of viral Meningitis. The range of ADA was between 1.2 to 15.4 U/L. At 10 U/L cut off value, sensitivity and specificity of the test for diagnosis of tuberculous meningitis was 95.65% and 96.29% respectively.CRP level in CSF was positive in all cases of pyogenic meningitis. All the 22 cases of viral meningitis and 23 cases of tuberculous meningitis showed a negative result for CRP.Many patients are needlessly receiving antitubercular treatment and antibiotics in high doses on erroneous interpretation of CSF. The tests for ADA and CRP in CSF are simple and can be carried out in a central laboratory with a rapid diagnosis, thus reducing undue delay or initiation of unwarranted harmful therapy for patients.*

Introduction

Infections involving the central nervous system, particularly meningitis and encephalitis are likely to arouse tremendous anxiety in both physician and the patients. The clinician must sort out the form of clinical presentation and make a specific etiological diagnosis with CSF analysis, Gram's staining, Ziehl-Neelsen staining, Latex agglutination tests, bacteriological and tuberculosis culture, viral diagnostic tests and PCR, the basis on which selection of potentially effective antimicrobial therapy is predicted. [1] Since each these techniques have their limitations, the search for more specific, sensitive, and rapid diagnostic methods continues.[2,3]

Reliable, cost effective, rapid screening tests like C Reactive Protein level and Adenosine Deaminase activity could be of much help in the differentiation of various types of meningitis in adults. Elevated CRP levels are highly suggestive of pyogenic meningitis. High ADA and normal CRP would make the diagnosis of TBM more convincing while negative ADA and CRP can strengthen the diagnosis of viral meningitis. Since false positive ADA may occur in pyogenic meningitis, a high CRP and ADA would favor the diagnosis of pyogenic meningitis thereby overcoming the false positive ADA.

This prospective study was designed to assess the significance of using both ADA and CRP levels in CSF as rapid screening tests to differentiate various types of meningitis.

Materials and Methods

This prospective study was conducted at Tirunelveli Medical College Hospital, Tirunelveli, and Tamil Nadu May' 2012 to October' 2012.The study protocol was approved by the Institutional Scientific and Ethics Committee.

Study population:

A total of 50 samples of CSF and Serum were collected from Patients attending in-patient departments of Tirunelveli medical college hospital with meningitis were taken for study. All the cases above 12 years of age with the following clinical signs like Fever, Neck Stiffness, Passive flexion of the neck and symptoms of meningeal infection were included for the study.

All patients underwent detailed history and thorough clinical examination. They were subjected to a battery of investigations which included Routine haemogram, CSF analysis, CSF- Gram stain and Ziehl Neelson staining, CSF- Culture and sensitivity and CT and other neuroimaging studies CSF ADA estimation.

CSF ADA was estimated in all patients by colorimetric method of GALANTI and GIUSTI[4].Reference values were taken as per the recommendations of Microxpress, a division of Tulip Diagnostics (P) Ltd. India, of which chemicals and reagents were used. ADA levels above 10 U/L were taken as positive.

CSF CRP estimation

C Reactive Protein in CSF was estimated based on latex agglutination. The presence of agglutination indicates concentration of CRP in the sample equal to or greater than 0.6 mg/dL.

Statistical analysis:

The collected data were edited for completeness, consistency and accuracy. They were analyzed by parameters like mean and percentages. The differences of the above parameter was tested by't' test and two sided chi test.

Results

A total of 50 patients with meningitis were analyzed, of which 28 were males and 22 were females. Age distribution data shows that maximum numbers of cases were seen in age group between 21 and 30 yrs. In the present study the lowest age was 15 years and highest age was 64 years.

Out of 50 cases, 46% cases were Tuberculous Meningitis, 10% was of Pyogenic Meningitis and 44% was of Viral Meningitis. TB meningitis occurred more in the younger age group and pyogenic meningitis was noted in the extremes of age group. The incidence of tuberculous and pyogenic

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meningitis was more in males and viral meningitis was more in females.

The range of ADA was between 1.2 to 15.4 U/L. ADA was > 10 U/L in 23 cases. ADA level in tuberculous meningitis was 10.4-15.4U/L with a mean level of 14.1 ± 1.96 (X ± SD) U/L. In pyogenic meningitis it was 3-10.1 U/L with a mean level of 4.92 ± 1.27 (X ± SD) U/L and in viral meningitis it was 1.2-4.9U/L with a mean level of 3.66 ±1.03 (X ± SD) U/L .ADA value was clearly higher in tuberculous meningitis than in pyogenic meningitis (t=3.9756, p<0.001, very highly significant) and viral meningitis (t=5.4513 p<0.001, very highly significant)

Table-1 Range of ADA with Mean Corresponding To Etiology

SL. NO.	ETIOLOGY	RANGE OF ADA	MEAN
1.	Tuberculous Meningitis	10.4-15.4	14.1 ± 1.96
2.	Pyogenic Meningitis	3-10.1	4.92 ± 1.27
3.	Viral Meningitis	1.2-4.9	3.66 ±1.03

Twenty two (95.65%) out of 23 patients with tuberculous meningitis had CSF ADA level > 10 U/L and only one (4.35%) had CSF ADA level < 10 U/L.Four (80%) out of 5 patients with pyogenic meningitis had CSF ADA level < 10 U/L and one (20%) had CSF ADA level > 10 U/L.All the 22 cases of viral meningitis had CSF ADA level < 10 U/L.

At 10 U/L cut off value, sensitivity and specificity of the test for diagnosis of tuberculous meningitis was 95.65% and 96.29% respectively while positive predictive value and negative predictive value was 95.65% and 96.29% respectively.

CRP estimation
CRP levels in CSF were positive in all cases of pyogenic meningitis. All the 22 cases of viral meningitis and 23 cases of tuberculous meningitis showed a negative result for CRP.

Table-2. Value of CRP in Meningitis

SL. NO.	ETIOLOGY	Value of CRP
1.	Tuberculous Meningitis	<0.6 mg/dl
2.	Pyogenic Meningitis	0.6 mg/dl
3.	Viral Meningitis	<0.6 mg/dl

Discussion
The earlier the recognition of the cause of meningitis and the more rapid the institution of appropriate therapy, the better the chance of a favorable outcome. Since the modality of treatment for bacterial, tuberculous and viral meningitis are totally different, it is very important to differentiate the meningitis on etiological basis.

Reliable, cost effective, rapid diagnostic tests which can be performed in any standard pathology laboratory could be of help in the differentiation of various types of meningitis in adults. In this regard, C reactive protein level and Adenosine deaminase activity can be used as rapid tests in the differential diagnosis of meningitis. ADA estimation is useful in diagnosis of tuberculous meningitis. However, the sensitivity of ADA has been found to be low due to the overlap in the ADA levels with pyogenic meningitis. CRP estimation has been documented to be helpful in diagnosing pyogenic meningitis and in increasing the sensitivity of ADA levels. The levels of both ADA and CRP are low in cases of viral meningitis.

There have been various studies on the use of ADA in tuberculous meningitis and CRP in pyogenic meningitis. Belagavi et al[5] observed that ADA activity was found to be the highest in tuberculous meningitis. At CSF ADA levels of 10 IU/L, the sensitivity and specificity of the test was 73.9% and 92.6% respectively with an accuracy of 84%. The sensitivity and specificity of CRP was 83.3% and 100% respectively with an accuracy of 98%.The NPV was 97.8, which implied that pyogenic meningitis could be ruled out if the CRP was negative.

Mishra et al [6] compared CSF ADA activity and CRP in tuberculous and partially treated bacterial meningitis in children. Based on this the sensitivity and specificity of ADA and CRP were 62.5%, 88.9% and 75%, 100% respectively.

With this background, the following prospective study was designed to assess the significance of using both ADA and CRP levels in CSF as rapid screening tests to differentiate various types of meningitis.

Out of 50 cases, 46% cases were Tuberculous Meningitis, 10% was of Pyogenic Meningitis and 44% was of Viral Meningitis.CSF ADA activities are raised in tuberculous meningitis and their use has been suggested to help differentiate tuberculous meningitis from viral and bacterial meningitis.[7]

Sang-Ho Choi et al [8] observed that mean ADA level in the tuberculous meningitis group was 12.7±7.5 U/l and it was significantly higher than the other groups. The sensitivity and specificity was 0.83 and 0.95 respectively when a cut-off value of 7U/l was used.

Pettersson et al[9] reported sensitivity of 1.0 and specificity of 0.99 when a cut-off value of 20 U/l was used, but in that study there were only 3 enrolled tuberculous meningitis patients.

In the present study, a total of 23 patients were diagnosed as tubercular meningitis based on the clinical features and CSF analysis. The mean ADA activity was 14.1 ± 1.96 U/l in the tuberculous meningitis group; 4.92 ± 1.27 in the pyogenic meningitis group; 3.66 ±1.03 in the viral meningitis group. Comparing the ADA activity in the three groups, the difference was found to be statistically significant (p<0.001) in the tuberculous meningitis group compared to the other groups. At 10 U/L cut off value, sensitivity and specificity of the test for diagnosis of tuberculous meningitis was 95.65% and 96.29% respectively while positive predictive value and negative predictive value was 95.65% and 96.29% respectively.

Apart from the routine CSF analysis which includes cell count, cell type, protein and sugar, CRP and ADA can also be used as rapid screening tests. Elevated CRP levels are highly suggestive of pyogenic meningitis. High ADA and normal CRP would make the diagnosis of TBM more convincing. On the other hand having both ADA and CRP negative can strengthen the diagnosis of viral meningitis. A high CRP in cases with high ADA would favor the diagnosis of pyogenic meningitis thereby overcoming the false positive ADA.

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