Cerebrospinal Fluid C Reactive Protein and Adenosine Deaminase in Meningitis in Adults

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Abstract

Objectives: To assess the utility of C-reactive protein (CRP) levels and adenosine deaminase (ADA) activity in the cerebrospinal fluid (CSF) as rapid screening tests to differentiate various types of meningitis in adults and to establish a cut off level for ADA.

Methods: CSF samples were obtained from 50 patients who presented to the emergency room and out-patient of Sri Siddhartha Medical Hospital, Tumkur during the period between August 2006 and September 2008. Diagnosis of meningitis was based on the clinical presentation and CSF analysis.

Results: Out of a total of 50 patients who were enrolled in the study, 24 were diagnosed as tubercular meningitis (TBM) based on the clinical features and CSF analysis. The mean Adenosine deaminase (ADA) activity was 14.1±4.4 U/l in the TBM group. The sensitivity and specificity was 71.7% and 92.6% respectively when a cut-off value of ADA of 10U/l was used, with an accuracy of 84%. CSF C Reactive protein (CRP) was significantly higher in pyogenic meningitis compared to non-pyogenic meningitis. The sensitivity and specificity of the test was 83.3% and 100% respectively with an accuracy of 98%.

Conclusions: 2 rapid screening tests- CRP and ADA activity in the CSF can help in the differential diagnosis of pyogenic from non-pyogenic meningitis and tuberculosis from viral meningitis respectively. CRP being elevated in pyogenic meningitis and ADA activity noted to be higher in TBM. The levels of ADA and CRP were found to be low in viral meningitis.

Background and Objectives

Infections involving the central nervous system, particularly meningitis and encephalitis are likely to arouse tremendous anxiety in both the physician and patients. Reliable, cost effective, rapid screening 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, CRP level and ADA activity can be used as rapid tests in the differential diagnosis of meningitis. ADA activity is useful in the diagnosis of TBM while CRP estimation has been documented to be helpful in diagnosing pyogenic meningitis. 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 TBM and CRP in pyogenic meningitis. However, no study has thus far utilized both ADA activity and CRP levels and compared their levels in the various types of meningitis. Mishra et al1 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.

We began this endeavor with the objective of using ADA and CRP levels in CSF as rapid screening tests to differentiate various types of meningitis and to establish a cut off level for ADA.

Materials and Methods

A total of 50 patients of suspected meningitis admitted to Sri Siddhartha Medical Hospital between August 2006 and September 2008 were included in the study. All patients were above 18 years of age with clinical features suggestive of meningitis. Those excluded from the study were patients with acute infections at sites other than the central nervous system, those in whom lumbar puncture was contraindicated and those with severe hepatic dysfunction and those with fungal meningitis.

Depending on the clinical and laboratory findings, patients were assigned to one of the following groups: (1) 5 cases of gram stain and culture positive cases of pyogenic meningitis; These patients had CSF analysis showing pleocytosis of >250 cells/mm³, protein >45mg/dl, sugar <40mg/dl or <40% of blood glucose concentration; (2) Patients with clinical and CSF laboratory findings consistent with TBM. Clinical features being the insidious onset of symptoms of meningitis, signs of meningeal irritation and presence of focal neurological deficits. The CSF analysis showing pleocytosis of >25 cells/mm³ predominantly lymphocytes, protein >45mg/dl, sugar <40mg/dl or <40% of blood glucose concentration. Neuroimaging showing evidence of meningeal enhancement, basal exudates or tuberculoma were supportive. These cases numbered 24; (3) 21 patients with viral meningitis based on clinical and CSF laboratory findings of lymphocytic pleocytosis of >25 cells/mm³, protein >45mg/dl and normal sugar.

CRP was estimated based on agglutination of the latex particles coated with anti-human CRP. The agglutination of the latex particles is proportional to the CRP concentration and is measured by turbidimetry.² ADA activity in CSF was determined at 37°C according to the method of Guisti and Galanti based on the Berthlot reaction and quantified spectrophotometrically.³ It takes half an hour of the CRP result to be available and a maximum of 4 hours for the result on ADA.
Table 1: Levels of CRP and ADA in different type of meningitis

<table>
<thead>
<tr>
<th>Type of meningitis</th>
<th>Number</th>
<th>CRP (mg/dl)</th>
<th>ADA (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBM</td>
<td>24</td>
<td>1.09±0.3</td>
<td>14.14±7.44</td>
</tr>
<tr>
<td>Pyogenic meningitis</td>
<td>5</td>
<td>27.00±13.78</td>
<td>9.80±13.66</td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>21</td>
<td>1.12±0.48</td>
<td>1.85±1.43</td>
</tr>
</tbody>
</table>

activity.

The increase in ADA in tuberculosis is due to increase in ADA2. It is required to determine the isoenzyme 1 and 2 of ADA if there is suspicion of malignancy, lymphoma or collagen vascular disease where ADA may be falsely elevated. The above were not in our differential when we were considering meningitis. Moreover, to estimate the precise quantity of ADA1 and ADA2 in a specimen, one should separate the two isoenzymes. This is complicated and expensive and hence was not done.

The HIV status was tested in all patients. There were 2 patients who were HIV positive having ADA values of 34IU/L and 10.2IU/L. The possibility of fungal meningitis was considered in them because of the overlap in the levels of ADA with fungal meningitis. The patient with ADA of 10.2 had CSF stain positive for KOH. This case was excluded from the study. The other patient who had a significantly high ADA of 4 was negative for fungal meningitis and eventually expired.

Statistical Methods

Descriptive statistical analysis has been carried out in the present study. Significance was assessed at 5 % level of significance. Binomial proportion test and Fisher Exact test has been used to find the significance of association of CRP and ADA levels with type of meningitis. Sensitivity, Specificity, PPV, NPV and Accuracy were calculated to know the diagnostic performance of CRP and ADA levels in relation to type of meningitis. 90% confidence interval has been calculated in the present study.

Results

A prospective clinical evaluation to study the predictive value of ADA and CRP in relation to various types of meningitis was undertaken.

ADA activity was found to be the highest in TBM. With the cut-off value of ADA of 10IU/L, the mean value was 14.14±7.44 IU/L. Patients with pyogenic meningitis had a mean ADA of 3.80±1.92 IU/L. The higher cut-off of ADA chosen helped overcome the overlap between tubercular and pyogenic meningitis. In addition, a low CRP favored the diagnosis of TBM.

CRP levels were elevated in pyogenic meningitis. The mean CRP level was 33±5.0 mg/dl. The patients with TBM and viral meningitis had a mean CRP level of 1.09±0.3 and 1.12±0.48 respectively.

The levels of CRP and ADA in the various types of meningitis have been compared in Table 1.

At CSF ADA levels of 10 IU/L, the sensitivity and specificity of ADA with respect to TBM was 73.9% and 92.6% respectively with an accuracy of 84%. This value was statistically significant with p<0.001. The sensitivity and specificity of CRP in relation to pyogenic meningitis in our study was 83.3% and 100% respectively. The NPV was 97.8, which implied that pyogenic meningitis could be ruled out if the CRP was negative. The accuracy of CRP for pyogenic meningitis was 98%. This result remained statistically significant with a p<0.001.

Discussion

The initiation of treatment in suspected cases of meningitis can often be delayed due to the lack of confidence in the presently available laboratory tests. Reliable, cost effective, rapid screening tests which can be performed in any standard pathology laboratory could be of help in the differentiation of various types of meningitis in adults especially in some places in India where resources are poor and when diagnostic tests can turn out negative.

Adenosine Deaminase (ADA)

The most commonly used laboratory method for the definitive diagnosis of TBM is to demonstrate the presence of tubercle bacilli either by smear and/or culture. However, direct smear methods are often negative in CSF samples and culturing of MTB takes 4-6 weeks to show the growth. Newer methods such as those involving the amplification of bacterial DNA by the PCR and comparable systems, are incompletely assessed and not available for widespread use. Hence, despite extensive work on TBM, only few diagnostic tests are available.

Therefore, there is a need for a rapid test that could be supportive in the diagnosis of TBM. Since early diagnosis and treatment can alter the outcome of these patients, ADA seems to be the appropriate test for this purpose.

CSF ADA activity is raised in TBM and their use has been suggested to help differentiate TBM from viral and bacterial meningitis.4-10

Kashyap et al did one of the largest studies on 117 patients of TBM and showed that the mean CSA ADA activity was found to be significantly higher in CSF of TBM patients, 14.3±3.87, than in the CSF from non-TBM infectious meningitis, 9.25±2.14.

Malan C et al showed that in both bacterial and TBM groups, the mean ADA level in the CSF was significantly higher than in aseptic meningitis (p<0.001). Similar results were noted in our study where the mean ADA value in viral meningitis was 1.85±1.43 which was well below the cut-off value.

In our study, we found that the mean value of CSF ADA was 3.80±1.92 in pyogenic meningitis. Some studies have reported a lower efficacy of this test and show an overlap between tuberculous meningitis and bacterial meningitis.22 So we used the higher cut-off value of 10 U/l in order to increase the sensitivity of ADA and overcome this lacuna. In addition, we combined it with a CRP, where low CRP favored the diagnosis of TBM.

As in previous studies (Table 2), it is apparent from the results of our study that the level of ADA in CSF was considerably elevated in TBM, the mean value being 14.14±7.44 IU/l compared to viral meningitis. This conclusion has proved to be extremely beneficial in the treatment of viral meningitis where patients have been started inadvertently on prolonged courses of anti tubercular medication with the misdiagnosis of TBM.

The patients neurological status at the time of admission was classified based on Glasgow Coma Scale (GCS) and the staging of TBM was established by the Medical Research Council (MRC). In stage 1, the patients were fully conscious and did not have any focal neurological deficits. In stage 2, patients were confused but not unconscious, or had focal neurological signs of localization such as hemiparesis or a single cranial nerve palsy. In stage 3, patients were stuporous or comatose or had multiple cranial nerve palsies or complete hemiplegia or paraplegia.
management of meningitis. But there are very few Indian meningitis and hence aid in the differential diagnosis and are higher in pyogenic meningitis compared to non-pyogenic meningitis. Large number of studies.

C Reactive Protein

Further, C reactive protein can help differentiate pyogenic from non-pyogenic meningitis. Large number of studies conducted around the world suggests that CRP levels in the CSF are higher in pyogenic meningitis compared to non-pyogenic meningitis and hence aid in the differential diagnosis and management of meningitis. But there are very few Indian studies.

A recent meta-analysis by Gerdes LU et al. suggested that a negative CRP test in either CSF or serum can be used with a very high probability to rule out bacterial meningitis.

In a study conducted by Vaishnavi C et al., CRP in CSF was significantly higher in patients with pyogenic meningitis compared to TBM. Authors concluded that the estimation of CRP in the differential diagnosis of meningitis might be made to give a preliminary diagnosis of meningitis.

The study by Hemavani V et al. concluded that CSF CRP determination can be of value to differentiate pyogenic versus other microbial meningitis etiology. However, it cannot differentiate between tuberculosis, fungal and viral meningitis.

In our study, the mean CRP in CSF of patients with pyogenic meningitis, tubercular meningitis and viral meningitis were; 33±5.0mg/dl, 1.09±0.3mg/dl and 1.12±0.48 respectively.

There was one case of fungal meningitis which was excluded from the study because previous studies and ours did show an overlap in the ADA activity and CRP levels. The case of fungal meningitis had a CRP of 12.00 and ADA of 10.2 U/l. However, KOH stain for candida was positive and the patient was retroviral positive as well. Hence differentiating tubercular and pyogenic meningitis from fungal meningitis was not difficult.

Either test done alone would still cause confusion in the probable diagnosis of meningitis, since the cell type in tubercular meningitis initially can predominantly be neutrophilic leukocytosis, in which case the diagnosis of tubercular meningitis is never entertained until the patient shows no response to the antibiotics. Patients with partially treated meningitis can have lymphocytic predominance when tubercular meningitis is wrongly considered. Viral meningitis can have lymphocytic predominance as well.

False positive ADA results were noted in cases of pyogenic meningitis. To overcome the fallacy, it is essential to do CRP as well simultaneously in order to increase the specificity of the test.

We suggest a protocol for the early differential diagnosis of meningitis using CSF ADA activity and CRP levels. In case of a patient with unexplained fever, headache, nausea/vomiting, a spinal tap with blood cultures is indicated if the CT scan brain is normal. 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. Tests for fungal meningitis could be restricted to those patients who are HIV infected where the suspicion of fungal meningitis is high.

Conclusion

Smear and/or culture for AFB, smear and culture for bacteria, India ink preparation, latex agglutination for antigens of bacteria or cryptococci remain the gold standard for diagnosis of various etiologies of meningitis. However, some of these tests especially for TBM and pyogenic meningitis can take time and may turn out negative. This is when physicians are in a diagnostic dilemma. Many patients are needlessly receiving antitubercular treatment and antibiotics in high doses on erroneous interpretation of CSF.

Early confirmatory diagnosis and aggressive management can help prevent serious CNS complications and at the same time reduce unwarranted or harmful therapy for patients. In this regard, two rapid screening tests-CRP and ADA activity in the CSF can help in the differential diagnosis of pyogenic from non-pyogenic and tubercular from viral meningitis respectively. CRP being elevated in pyogenic meningitis and ADA activity noted to be higher in tuberculous meningitis. The levels of ADA and CRP are low in viral meningitis. 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 unwarranted or harmful therapy for patients. However, these tests should be interpreted judiciously in the light of the patients’ clinical manifestations and the CSF characteristics.

This study emphasizes the need to raise the awareness about using the 2 rapid tests like CRP and ADA for diagnosing meningitis and to encourage more studies with larger sample size in this regard.

References


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