Rapid Diagnostic Test for the Discrimination between Types of Meningitis

Nishant Pujara*, Vachan Mehta, Kinnari Thacker***, Jay Shah******

* Associate Professor, ** Assistant Professor, Department of Medicine, Gujarat Adani Institute of Medical Science, Bhuj,
Tutor, Department of Anatomy, * Tutor, Department of Pharmacology, M K Shah Medical College, Ahmadabad, Gujarat

Abstract: Background & Aim: there is a need for an easy and comprehensive test to diagnose Acute Bacterial Meningitis timely. Routine use of CSF CRP in diagnosing acute bacterial meningitis could be a rapid, reliable and easy method for diagnosis of meningitis. Hence the aim of this study is to evaluate whether C-reactive protein and adenosine deaminase levels could be used to differentiate the various types of meningitis in adults. Methods: Patients were divided into three groups. Group I comprised of 10 cases of pyogenic meningitis based on clinical features usually acute in onset. They were associated with otitis media, sinusitis and signs of meningeal irritation. Group II comprised of 62 cases of tuberculosis meningitis, which included insidious in onset, maybe associated with TB of other organs or signs of meningeal irritation. Group III comprised of 18 cases of viral meningitis based on clinical presentation, usually acute in onset with signs of meningeal irritation. Results: CRP level in pyogenic meningitis cases were found to be significantly higher as compared to the other two groups. It was found that none of the cases of pyogenic and viral meningitis had positive ADA values. Conclusion: On the basis of above based result and discussion it was concluded that ADA activity in CSF is elevated in tuberculous meningitis. CSF-CRP levels can reliably discriminate between pyogenic and non-pyogenic meningitis. [N Pujara Natl J Integr Res Med, 2018; 9(1):12-15]

Key Words: ADA, CSF, Evaluation, Meningitis

Author for correspondence: Vachan Mehta, 28, New Nirmalsinh Wadi, Near Pramukhswami Temple, Bhuj,Kutch,Gujarat-370001 E-Mail: researchguide86@gmail.com M: 9427350988

Introduction: Meningitis is an inflammation of the membranes (meninges) surrounding your brain and spinal cord. The swelling from meningitis typically triggers symptoms such as headache, fever and a stiff neck. Most cases of meningitis in the U.S. are caused by a viral infection, but bacterial and fungal infections are other causes.[1] Young children often exhibit only nonspecific symptoms, such as irritability, drowsiness, or poor feeding. If a rash is present, it may indicate a particular cause of meningitis; for instance, meningitis caused by meningococcal bacteria may be accompanied by a characteristic rash.[2] Some cases of meningitis improve without treatment in a few weeks. Others can be life-threatening and require emergent antibiotic treatment. Seek immediate medical care if you suspect that someone has meningitis. Early treatment of bacterial meningitis can prevent serious complications.[3]

Cerebrospinal Fluid (CSF) Gram stain and culture is the gold standard for diagnosis of pyogenic meningitis. However only 30-60% of pyogenic meningitis cases are culture positive.[4] Moreover the procedure requires skill, is costly and time consuming (preliminary results are delayed for at least 48 hours). Lactate in CSF normally parallels blood levels, but with biochemical alteration of CNS, CSF lactate value changes independent of blood values. A number of factors may contribute to the elevated concentration of CSF lactate. The increase maybe due to any of the following- the presence of leucocytes, organisms or increased production by cerebral tissue secondary to hypoxia.[5]

C - reactive protein (CRP) is an acute phase reactant. Almost any inflammation in the body causes CRP to be detected in serum or other body fluids associated with the affected tissues. In Western countries, attention has been directed to the value of serum CRP values to differentiate bacterial and viral infections. Few studies have reported CSF C-reactive protein to have high sensitivity and specificity in differentiating pyogenic meningitis from aseptic meningitis.[6]

ADA hydrolyses adenosine to ammonia and inosine. The ammonia formed further reacts with phenol and hypochlorite in an alkaline medium to form blue indophenol complex with sodium nitroprusside acting as a catalyst. Intensity of the blue is proportional to the amount of ADA. Adenosine + H2→Inosine + ammonia. Ammonia + phenol + hypochlorite Blue indophenols.[7]

India is a developing country, with limited resources and skilled manpower particularly in peripheral set up. Hence there is a need for an easy and comprehensive test to diagnose Acute Bacterial Meningitis timely. Routine use of CSF CRP in diagnosing acute bacterial meningitis could be a rapid, reliable and easy method

for diagnosis of meningitis. Hence the aim of this study is to evaluate whether C-reactive protein and adenosine deaminase levels could be used to differentiate the various types of meningitis in adults.

Methods: This hospital based prospective case controlled study was conducted in Department of medicine for a period of one year. All children between 1 month to 18 years of age admitted with acute history of fever and seizure were included in the study after taking a written informed consent. Ethical committee of the institution were informed about the study and ethical clearance certificate was obtained from the committee. Children who received antibiotic for more than 24 hours before CSF study or had congenital central nervous system abnormality or suffering from any chronic illness, greater than 18 years, patient with acute infections at sites other than central nervous system, in whom lumbar puncture is contraindicated, patients on steroids and with fungal meningitis were excluded from the present study.

Patients were divided into three groups. Group I comprised of 10 cases of pyogenic meningitis based on clinical features usually acute in onset. They were associated with otitis media, sinusitis and signs of meningeal irritation. Group II comprised of 62 cases of tuberculosis meningitis, which included insidious in onset, maybe associated with TB of other organs or signs of meningeal irritation. Group III comprised of 18 cases of viral meningitis based on clinical presentation, usually acute in onset with signs of meningeal irritation.

CRP was determined qualitatively by rapid slide latex agglutination method using diagnostic kits supplied by Span Diagnostics Limited. C - reactive protein (CRP) >6mcg/ml was considered as a positive test. Study Design- A prospective clinical evaluation study is undertaken to study the predictive value of CRP and ADA in relation to various types of meningitis.

Statistical Analysis: Qualitative data will be expressed as percentages and proportions. Quantitative data will be expressed as mean and standard deviation. The differences between two groups with respect to continuous variables will be analysed using t-test while categorical variables will be analysed using chi-square test. All the statistical tests will be performed in SPSS version 15 software. P value <0.05will be considered as statistically significant while P value<0.01 will be considered as statistically highly significant. The between group comparison of compressive strength of samples in Group A and B was done using One- way ANOVA test. Within group comparison was done using Bonferroni correction test. In the tests, p value of ≤0.05 was considered as statistically significant.

Results: As per the observation of the study we found that we have high case number of tuberculosis bacterial meningitis which was followed by viral and pyogenic meningitis. The percentage of TBM being 72%, viral meningitis 18% and pyogenic meningitis 10%. In our present study, we had high incidence of TBM in males as compared to females similar results were obtained from pyogenic and viral meningitis group. However when the statistical test were applied, the difference was not found to be significant.

Table 1: Distribution of types of Meningitis

Type of Meningitis	Number	Percentage
Pyogenic Meningitis	10	10
TBM	72	72
Viral Meningitis	18	18
Total	100	100

Table 2: Distribution of sex in our study

Type of Meningitis	Male	Female	Total	P value
Pyogenic Meningitis	8	2	28	0.067
Tuberculosis Meningitis	62	10	72	
Viral Meningitis	10	8	18	
Total	80	20	100	

P< 0.05: statistical significant.

When the CRP levels were evaluated in all three groups. They were found to be elevated in pyogenic meningitis. The highest CRP level in our study was found to be 33.2 ± 5.12 mg/dl, which was found in Pyogenic meningitis group. The patient with tuberculosis and viral meningitis had a mean CRP level of 3.01 ± 3.69 mg/dl and 2.10 ± 0.21 mg/dl respectively. In all the cases of pyogenic meningitis, the values of CRP levels were more than cut off value, i.e. 20 mg/dl. Onl2 cases in tuberculosis meningitis had more than cut off value for CRP levels. In viral meningitis, no cases had positive CRP value. When the stats were applied the positive CRP level in pyogenic

meningitis cases were found to be significantly higher as compared to the other two groups.

Table 3: CRP values in different groups

Groups	No. of cases	CRP (mg/dl)	CRP > 20 mg/dl	
			No.	P value
Pyogenic Meningitis	10	33.2 ± 5.12	10 (100%)	0.001
Tuberculosis Meningitis	72	3.01 ± 3.69	2 (2%)	-
Viral Meningitis	18	2.10 ± 0.21	-	-
Total	100	-	12	

P value < 0.05 is considered as significant

When the levels of ADA were evaluated in different groups of the study. Highest ADA level were found in tuberculosis meningitis with value of 15.14 ± 10.2, it was followed by pyogenic and viral meningitis with value recorded as 4.1 ± 2.10 U/L and 2.12 ± 0.78 U/L. However the higher values obtained was utilized in separating the over lapped cases of pyogenic and tuberculosis meningitis. The cut off value of ADA was found to be 9 U/L. It was found that none of the cases of pyogenic and viral meningitis had positive ADA values.

Table 4: ADA levels in various types of meningitis

Groups	No. of cases	ADA (U/L)	ADA > 9 U/L	
			No.	P value
Pyogenic Meningitis	10	4.1 ± 2.10	-	-
Tuberculosis Meningitis	72	15.14 ± 10.2	52 (52%)	0.0002
Viral Meningitis	18	2.12 ± 0.78	-	-
Total	100	-	52	

P value < 0.05 is considered as significant

Discussion: Bacterial meningitis is a life-threatening illness. Early recognition and appropriate antibiotic treatment is crucial to reduce morbidity and mortality. In developing country like India facilities to appropriately isolate blood- or CSF-borne organisms is scarce and if available culture reports are time consuming.[8] There is a requirement of a test which is easy, quick, cheap and reliable to diagnose the aetiology of meningitis at the bedside. CSF-CRP and ADA tests meets all this criterion and unlike CSF cytology and biochemistry does not require a lot of knowledge to interpret the results.

Adenosine deaminase is an enzyme involved in purine catabolism leading to hydrolysis and deamination of adenosine to inosine and ammonia. ADA has shown promising results in diagnosis of tuberculous pleural, peritoneal and pericardial effusion and tuberculous meningitis.[9] C-reactive protein is a marker of acute phase response or inflammation. Usage of CRP in differentiating pyogenic and non-pyogenic meningitis has been documented. CSF-ADA levels are raised in tuberculos meningitis and their use has been suggestive of differentiating tuberculous meningitis from viral and bacterial meningitis. Similar results were obtained by Choi et al; the mean ADA level in tuberculos meningitis group was 12.7 ± 7.5 U/L and it was significantly higher than the other groups.[10]

The test for ADA in CSF is simple and can be carried out in a central laboratory with a rapid diagnosis, thus reducing unwarranted or harmful therapy for patients. The finding of our study is that CSF-CRP is significantly higher in pyogenic meningitis compared to non-pyogenic meningitis. This result remained statistically significant with p<0.05. in the previous study done by Goran Rajs et al it was found that CRP levels were higher in gram negative pyogenic meningitis as compared to gram positive pyogenic meningitis. This suggests that infection with gram negative bacteria do enhances the permeability of CRP through the blood brain barrier. A recent meta-analysis by Gerdes LU et al[11] suggested that a negative CRP test in either CSF or serum can be used with a very high probability to rule out bacterial meningitis.

Conclusion: On the basis of above based result and discussion it was concluded that ADA activity in CSF is elevated in tuberculous meningitis. CSF-CRP levels can reliably discriminate between pyogenic and non-pyogenic meningitis.

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