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Original Research Article

Rapid differential diagnostic methods of meningitis in adults

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ABSTRACT

Background: Acute infections of the nervous system are among the most importantproblems in medicine because early recognition, efficient decision making, and rapid institution of therapy can be lifesaving. Objective of the present study was to find out the usefulness of these two tests, CSF-ADA and CSF-CRP for the rapid diagnosis and differentiation of bacterial, tubercular and viral meningitis in adults.
Methods: Fifty meningitis patients were selected after fulfilling the following inclusion and exclusion criteria. A prospective clinical evaluation study is undertaken to study the predictive value of CSF CRP and ADA in relation to various types of meningitis.
Results: More than half the cases reported were of tubercular meningitis, followed by viral and pyogenic meningitis. The percentages of tubercular, viral and pyogenic were 52%, 32% and 16% respectively. CRP levels were elevated in pyogenic meningitis; the mean CRP level was 25.26±5.56 mg/dl. ADA activity was found to highest in tubercular meningitis, the mean value was 17.67±8.13 IU/L.
Conclusions: Study concluded that combine use of CSF CRP and ADA can be used for early differentiation of bacterial, tubercular, and viral meningitis.

Keywords: ADA (adenosine deaminase), CSF (cerebrospinal fluid), CRP (C reactive protein), ICP (Intracranial pressure)

INTRODUCTION

Acute infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision making, and rapid institution of therapy can be lifesaving. Each may present with a nonspecific prodrome of fever and headache, which in a previously healthy individual.

Meningitis is an acute purulent infection within the subarachnoid space. It is associated with a CNS inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke. The meninges, subarachnoid space, and brain parenchyma are all frequently involved in the inflammatory reaction (meningoencephalitis).[1]

Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days.[1]

The classic clinical triad of meningitis is fever, headache, and nuchal rigidity, but the classic triad may not be present. A decreased level of consciousness occurs in >75% of patients and can vary from lethargy to coma. Fever and either headache, stiff neck, or an altered level of consciousness will be present in nearly every patient with bacterial meningitis. Nausea, vomiting, and photophobia are also common complaints.[1]

The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients

with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases.[1]

Among the patients with meningitis, tubercular meningitis remains an important cause of morbidity and mortality in India. Tuberculosis of the central nervous system accounts for ~5% of extrapulmonary cases in the United States. With the lack of early diagnosis, fatality remains high, sequelae may be distressing and disabling in the non-fatal cases. Adenosine deaminase activity has shown promising results in the diagnosis of tubercular pleural, peritoneal and pericardial effusion and tubercular meningitis.[2]

Viral meningitis is not a nationally reportable disease; however, it has been estimated that the incidence is ~60,000–75,000 cases per year. Intemperate climates, there is a substantial increase in cases during the non-winter months, reflecting the seasonal predominance of entero virus and arthropod-borne virus (arbo virus) infections in the summer and fall, with a peak monthly incidence of about 1 reported case per 100,000 population.[1]

CRP is one of the most sensitive of the acute phase response with plasma levels rising up to 2000-fold after infection. Levels are in general much higher in bacterial than viral infections. The increase with inflammation occurs within 6 to 12 hours and peaks at about 48 hours. It is generally proportional to the degree of tissue damage.[3]

In view of such observations, the present study was conducted to find out the usefulness of these two tests, CSF-ADA and CSF-CRP for the rapid diagnosis and differentiation of bacterial, tubercular and viral meningitis in adults.

METHODS

A prospective clinical evaluation study is undertaken to study the predictive value of CSF CRP and ADA in relation to various types of meningitis. Meningitis patients admitted and willing to give consent in the Medicine Department at Victoria hospital and Bowring and Lady Curzon hospital , BMCRI, Bangalore.

The study was approved by the Ethical Committee of Bangalore Medical College and Research Institute, Bangalore. 50 Meningitis patients were selected after fulfilling the following inclusion and exclusion criteria.

Inclusion criteria

Age > 18 years, clinical features suggestive of meningitis were included in the study.

Exclusion criteria

Age < 18 years, patients on steroid, patient with acute infections at sites other than central nervous system, females on oral contraceptives and intrauterine device, patients in whom lumbar puncture is contraindicated, severe dyslipidemia, associated severe hepatic dysfunction were excluded from the study.

After taking written informed consent, Demographic data, detailed history, physical and systemic examination was recorded. All blood Investigations including complete heamogram, LFT, RFT, RBS, serum electrolytes, HIV test, chest X-ray, CT brain (plain) were recorded. CSF cytology, biochemistry, gram stain, AFB stain, and culture was done. An estimation of CSF ADA and C-reactive protein level was done for all the patients satisfying the inclusion and exclusion criteria. These cases were further divided in to 3 groups.

Group I- Bacterial meningitis

This group included 08 Patients with clinical and CSF laboratory findings consistent withBacterial meningitis.

Clinical features

Acute onset of symptoms of meningitis, may be associated with sinusitis, otitis media, and signs of meningeal irritation.

CSF analysis showing

Pleocytosis of >250 cells/mm^3, predominantly neutrophils.
Proteins > 50mg/dl.
Sugar < 40mg/dl.
Gram stains and culture positivity.

Neuroimaging showing

Evidence of diffuse meningeal enhancement, abscesses or parameningeal focus.

Group II- Tubercular meningitis

This group included 26 Patients with clinical and CSF laboratory findings consistent with Tubercular meningitis.

Clinical features

Insidious in onset, may be associated with tuberculosis of other organs, signs of meningeal irritation.

CSF analysis showing:

Pleocytosis of >60 cells/mm3, predominantly lymphocytes.
Proteins >40mg/dl.
Sugar< 40mg/dl.
AFB stain or culture positive.

Neuroimaging showing

Evidence of Meningeal enhancement, basal exudates and/or tuberculoma.

Group III-Viral meningitis

This group included 16 Patients with clinical and CSF laboratory findings consistent with VM.

Clinical features

Usually acute in onset with signs of meningeal irritation.

CSF analysis showing

Pleocytosis of >25 cells/mm^3, predominantly lymphocytes.
Proteins > 45mg/dl.
Sugar - normal.

Neuroimaging

Diffuse meningeal enhancement.

Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented in Mean SD (Min- Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. The Statistical software namely SAS 9.2, SPSS 15.0, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

50 meningitis patients who were admitted in Department of Medicine, Victoria hospital and Bowring and Lady Curzon hospital were included in this cross sectional study.

Table 1: Age distribution of patients.

Age (years)	Tubercular meningitis	Viral meningitis	Pyogenic meningitis	Total	In percentage
18-20	02	02	01	05	10
21-40	15	09	04	28	56
41-60	05	05	03	13	26
>60	04	00	00	04	8
Total	26	16	08	50	100
In percentage (%)	52	32	16	100	

Table 2: Gender distribution of meningitis.

Gender	Tubercular meningitis	Viral meningitis	Pyogenic meningitis	Total	Percentage
Male	16	04	06	26	52%
Female	10	12	02	24	48%
Total	26	16	8	50	100
Percentage (%)	52	32	16	100	

Table 3: Distribution of types of meningitis.

Type of meningitis	Number	Percentage
Tubercular meningitis	26	52
Viral meningitis	16	32
Pyogenic meningitis	8	16
Total	50	100

The mean age of the 50 patients studied was 37.76±15.58 years. The youngest patient was 19 years old and oldest patient was 75 years. 56% (n=28) of patients in the study were aged between 21-40 years with the maximum number of patients (n=15) being tubercular meningitis (Table 1). In this study, 52% were male and 48% were female. Viral meningitis was more common in females compared to males, percentages being 24% and 08% respectively. The incidence of tubercular and pyogenic meningitis was more in males (Table 2).

More than half the cases reported were of tubercular meningitis, followed by viral and pyogenic meningitis. The percentages of tubercular, viral and pyogenic were 52%, 32% and 16% respectively (Table 3).

Table 4: Viruses causing meningitis.

Common	Less common	Rare
Enteroviruses	HSV -1	Adenoviruses
Arboviruses	LCMV	CMV
HIV	VZV	EBV
HSV-2		Influenza A,B Para influenza, Mumps, Rubella

Mean polymorphs count was significantly higher in pyogenic meningitis (91.5±4.74%), compared to tubercular (17.96±29.26%) viral (9.75±12.15%) meningitis.

Table 5: Typical CSF profiles for meningitis.

	Normal	Bacterial meningitis	Tubercular meningitis	Viral meningitis
Opening pressure (mm of H_2O)	50-180	>300	150-280	100-350
WBC count (per microL)	<5	>1000	25-100	25-500
Differential of WBC	60-70% lymphocytes, ≤30% monocytes/macrophages	Increased PMNs (≥80%)	Predominantly lymphocytes	Predominantly lymphocytes
Gram's stain	Negative	Positive (in >60% of cases)	Occasionally positive	Negative
Glucose (mg/dl)	40-85	<40	<50 in 75% of cases	Normal
Protein (mg/dl)	15-45	>100	100-200	20-80
Common causes	-	Streptococcus pneumoniae, Neisseria meningitidis	Mycobacterium tuberculosis	Enteroviruses

Abbrevations : PMNs – Polymorphonuclear neutrophils; WBC– White blood cell.

The mean lymphocyte count in tubercular and viral meningitis was 82.03±29.26% and 89.31±12.32% respectively, Z=1.117; p≤0.267 which is not statistically Significant. In pyogenic meningitis mean lymphocyte count was 8.5±4.79%.

Mean protein in tubercular and pyogenic meningitis is 198.42±130.97 mg/dl and 291.375±102.88 mg/dl respectively, Z=2.087; p≤0.037 which is moderately Significant. CRP levels were elevated in pyogenic meningitis, the mean CRP level was 25.26±5.56 mg/dl. The patients with tubercular and viral meningitis had mean CRP level of 0.88±0.64 mg/dl and 0.43±0.37 mg/dl respectively.

ADA activity was found to be the highest in tubercular meningitis, the mean value was 17.67±8.13 IU/L. Patients with pyogenic meningitis had mean ADA of 2.95±6.7 IU/L. Z=12.38 P≤0.001 which is statically significant.

DISCUSSION

Much of the pathophysiology of meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF-α and IL-1β act synergistically to increase the permeability of the blood-brain barrier, resulting in induction of vasogenic edema and the leakage of serum proteins into the subarachnoid space. The subarachnoid exudate of proteinaceous material and leukocytes obstructs the flow of CSF through the ventricular system and diminishes there sorptive capacity of the arachnoid granulations in the dural sinuses, leading to obstructive and communicating hydrocephalus and concomitant interstitial edema.[1]

Common viruses causing meningitis include enterovirus, arboviruses, HIV, HSV-2. Typical CSF profiles in different types of meningitis (Table 5).

C-reactive protein can help to 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.[5-9] But there are very few Indian studies.

The results of the present study shown that CRP level was significantly increased in bacterial meningitis as compared to tubercular and viral meningitis. Mean value of CRP in pyogenic, tubercular and viral meningitis was 25.26±5.56 mg/dl, 0.88±0.64 mg/dl and 0.43±0.37 mg/dl respectively. This result remained statistically significant with p<0.001. The sensitivity and specificity of the test was 100% and 100% respectively with an accuracy of 100% in relation to pyogenic meningitis.

Hemavani et al evaluated the role of CRP in CSF in differentiation of meningitis. The study included 499 CSF samples from cases of viral, pyogenic, tuberculous and fungal meningitis and 580 normal CSF samples. CRP positive by qualitative latex agglutination test was seen in 73.3% of CSF samples from partially treated pyogenic meningitis and 92% among pyogenic meningitis cases. All suspected cases of tuberculosis meningitis were negative for CRP in the CSF while only 1 out of CSF samples for bacteriologically confirmed tuberculous meningitis was positive. CRP was raised in 27.2% and 12.5% of CSF samples from candidal and cryptococcal meningitis cases respectively, while none of the 102 samples from suspected viral meningitis and 580 non-meningitis cases were positive for CRP in the CSF. The study concludes 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.[7]

In a study conducted by Vaishnavi et al, CRP in CSF was significantly higher in patients with pyogenic meningitis compared to tubercular meningitis. Authors concluded that the estimation of CRP in the differential diagnosis of meningitis might be made to give a preliminary diagnosis of meningitis.[10]

Previous studies conducted by Rajs et al, have observed that CSF-CRP levels are higher in gram-negative pyogenic meningitis compared to gram positive pyogenic meningitis suggesting that infection with gram-negative bacteria probably enhances permeability of CRP through blood brain barrier.[11,12]

Another study conducted by Rajamani et al, 100% of patients of pyogenic and tubercular meningitis has serum CRP above 12 mg/dl but patients of pyogenic meningitis has levels above 96mg/L. CSF-CRP sensitivity was found in 83.33% cases of pyogenic and none from tubercular meningitis or viral meningitis. CSF - CRP level in pyogenic meningitis were very high (104±90.21 mg/dl) but within normal range in tubercular meningitis, viral meningitis and controls (< 6mg/dl).[9]

Present study found that ADA level was significantly increased in tubercular meningitis as compared to bacterial and viral meningitis. The mean value of ADA was in tubercular meningitis (17.67±8.13 IU/L), pyogenic meningitis (2.95±6.7 IU/L) with Z=12.38 p≤0.001 which is statically significant. Mean ADA level in viral meningitis was 1.89±0.55 IU/L.

Choi et al studied ADA activity in CSF of 182 patients with meningitis. The mean ADA level in the tuberculous meningitis group was 12.7±7.5 U/L and it was significantly higher than the other groups (3.10±2.9U/l; p<0.001). The sensitivity and specificity was 0.83 and 0.95 respectively when a cut-off value of 7U/L was used.[14]

Gambhir et al found that the mean CSF ADA levels in TBM patients was 9.61±4.10 U/l and was significantly elevated as compared to viral encephalitis and enteric encephalopathy cases; but the difference was insignificant in comparison to pyogenic meningitis and cerebral malaria.[13]

CONCLUSION

Study concludes that combine use of CSF CRP and ADA can be used for early differentiation of Bacterial, Tubercular, and Viral meningitis. These 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.

CSF-CRP levels were higher in pyogenic meningitis than in non-pyogenic meningitis. CSF ADA activity was higher in patients with tubercular meningitis when compared to pyogenic and viral meningitis.

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