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To study serum c-reactive protein levels in differentiating bacterial meningitis from viral meningitis

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Abstract

Introduction: Meningitis is a clinical syndrome characterized by inflammation of meninges. The classic triad of meningitis consists of fever, headache and neck stiffness. Pneumococcal meningitis is the most common bacterial cause of meningitis. Most patients recover completely if appropriate antibiotic therapy is instituted promptly. Tubercular meningitis is a very critical disease in terms of fatal outcome and permanent sequelae, requiring rapid diagnosis and treatment. Death may occur as a result of missed diagnosis and delayed treatment. Enterovirus is the most common cause of viral meningitis. Cryptococcal meningitis may be seen especially in persons with defective cell mediated immunity. Encephalitis primarily involves the brain; it often involves the meninges as well (meningoencephalitis). This study is done to emphasize the importance of early diagnosis, so that prompt management is given at appropriate time.

Aim: This is a prospective observational, single center study done in Department of medicine NSCB medical college hospital Jabalpur in 93 patients of acute meningoencephalitis cases: 1st March.2020 to 31 August 2021. The main aim of this study is 'To study serum c-reactive protein levels in differentiating bacterial meningitis from viral meningitis"

Materials And Methods: In the present study, we recruited 93 patients who presented with meningitis and meningoencephalitis who fulfilled the inclusion criteria. Proforma is used to collect data needed. Data are statistically analysed.

Results: Among the 93 patients with meningo-encephalitis in this study, the common initial presenting symptoms were fever (89%) and Vomiting (89%) >altered sensorium> headache and neck pain and stiffness>Focal neurological deficit> seizure. Fever was the most common initial presenting symptom. 86 patients (92.5%) had fever and headache (92.5%). 31 patient was found as bacterial meningitis which had s-crp value mostly ranging between >24 mg/l, out of them 19 patient had s-crp value >48 mg/l (61.29%). Most of them had poor prognosis and presented with altered sensorium and high-grade fever. most of the case out of 37 had s-crp value between intermediate range (12-48) mg/l and 2 patients had range between >48 mg/l which had miliary tuberculosis.

Conclusion: In the present study we found that, most of the patients with meningoencephalitis were males and young adults. Surprisingly, tuberculous meningitis was the most common overall cause in our study. Both viral meningo-encephalitis and pyogenic meningitis constituted most of the cases of acute Meningo-encephalitis. Tuberculous meningitis was the most common cause in patient with subacute meningitis. All patients with chronic presentation had tuberculous meningitis. We came across atypical presentation of cryptococcal meningitis in a non-HIV patient. 47 patients recovered well without neurological deficits. Estimation of C-reactive protein in serum is the cheapest, sensitive and specific test to differentiate bacterial from viral infections. It is a simple qualitative as well as quantitative test and can be done as a bed side investigation. With serum C-reactive protein, a definite etiological diagnosis can be made rapidly at the time of admission itself.

Keywords: c-reactive protein, meningo-encephalitis, tuberculosis

Introduction

Meningitis is a clinical syndrome characterized by inflammation of meninges. The classic triad of meningitis consists of fever, headache and neck stiffness1. Bacterial meningitis occurs in about 3 people per 100,000 annually in western countries. Population-wide studies have shown that viral meningitis is more common at 10.9 per 100,0002 population.

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Bacterial (pyogenic) meningitis is a pyogenic inflammation of meninges and subarachnoid cerebrospinal fluid (CSF) and is characterized by neutrophilic pleocytosis in CSF3. Pneumococcal meningitis is caused by streptococcus pneumonia, a gram-positive coccus and is the most common bacterial cause of meningitis. Meningococcal meningitis is caused by gram-negative diplococcus - Neisseria meningitides. Most patients recover completely if appropriate antibiotic therapy is instituted promptly3.

Tubercular meningitis is a very critical disease in terms of fatal outcome and permanent sequelae, requiring rapid diagnosis and treatment4. Tuberculous meningitis should be a strong consideration when a patient presents with clinical picture of meningoencephalitis, especially in high-risk groups, including persons with malnutrition, those with abuse alcohol or drugs and patients with known retroviral infection. Death may occur as a result of missed diagnosis and delayed treatment5.

World-wide causes of viral meningitis include enterovirus, herpes, mumps, measles and HIV. Enterovirus is the most common cause of viral meningitis.

Aseptic meningitis is an illness characterized by serious inflammation of the meninges, usually with an accompanying CSF lymphocyte pleocytosis. Clinical manifestations vary with headache and fever predominating. The illness is usually mild and runs its course without treatment, however some cases can be severe and life threatening.

Remarkable recovery may be achieved in some patients with viral meningitis who become even comatose. Vigorous supportive therapy and avoidance of complications are very important in managing these patients6.
Cryptococcal meningitis is caused by the yeast Cryptococcus neoformans, especially in persons with defective cell mediated immunity. Prompt antifungal therapy should be considered in these patients7.

The incidence of acute encephalitis in western countries is 7.4 per 100,000 population per year. In tropical countries like India, it is 6.4 per 100,000 per year. Herpes simplex encephalitis has an incidence of 2-4 per million population per year.

Encephalitis presents as diffuse or focal neuropsychological dysfunction although it primarily involves the brain, it often involves the meninges as well (meningoencephalitis). From an epidemiologic and pathophysiologic perspective encephalitis is distinct from meningitis, though on clinical evaluation both can be present, with signs and symptoms of meningeal inflammation. The prodrome typically consists of fever, headache, nausea, vomiting, lethargy and myalgias.

The clinical presentation is encephalopathy with diffuse or focal neurological symptoms including behavioral and personality changes, with decreased level of consciousness, neck pain/stiffness, photophobia, lethargy, generalized or focal seizures, acute confusion or amnestic states and flaccid paralysis8.

There are no studies done till now showing the clinical, etiological and outcome in patients with meningitis and meningoencephalitis. There are some studies done in children but not in adults.

Distinguishing the etiologies also helps in terms of both reducing antibiotic usage and hospital bed occupancy and reassuring contacts of cases and health care staff of a non-bacterial cause.

As there are fewer developments in therapies for viral meningitis and there remain no effective therapies for most pathogens, this study is done to emphasize the importance of early diagnosis, so that prompt management is given at appropriate time.

Aims & Objective

This is a prospective observational, single center study done in Department of medicine NSCB medical college hospital Jabalpur in 93 patients of acute meningoencephalitis cases: 1st March.2020 to 31 August 2021. The main aim of this study is 'To study serum c-reactive protein levels in differentiating bacterial meningitis from viral meningitis''

Inclusion criteria:

- Patients fulfilling the diagnostic criteria for encephalitis
- People willing to give consent for CSF lumber puncture

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- Age more than 14 years

Exclusion criteria:

- People not willing to give consent for CSF lumber puncture
- Age criteria less than 14 year of age
- Known case of Rheumatic heart disease (According to modified Jones criteria)
- Patients with organic central nervous system disease, endocrine disorders, uremia, severe electrolyte disturbances, and drug reactions

Materials & Methods

This prospective observational study will be carried out in the department of medicine NSCB medical college hospital Jabalpur. We intend to enroll at least 93 of acute meningoencephalitis attending the outpatient department as well as getting admitted in the wards of department of medicine of our college. This study will be approved by institutional ethical committee and written informed consent will be obtained from all participants before inclusion in the study.

All patients fulfilling the following criteria will be enrolled
Major Criteria (required)
Patients presenting to medical attention with altered mental status (defined decreased or altered level of consciousness, lethargy or personality changes) lasting more than 24 hours with no alternative cause identified.
Minor Criteria (2 required for possible encephalitis,>3 required for probable or confirmed encephalitis)

1. Documented fever 38 degree Celsius (100.4-degree Fahrenheit) within 72 hours before or after presentation
2. Generalized or partial seizures not fully attributable to a preexisting seizure disorder.
3. New onset of focal neurologic findings.
4. CSF WBC count >5/cumm
5. Abnormality of brain parenchyma on neuroimaging suggestive of meningoencephalitis that is either new from prior studies or appear acute in onset.
6. Abnormality on EEG that is consistent with encephalitis and not attributable to another cause.

Result And Interpretation Positive Results

The presence of agglutination indicates concentration of CRP in the sample equal to or greater than 0.6 mg/dL.

Negative Results

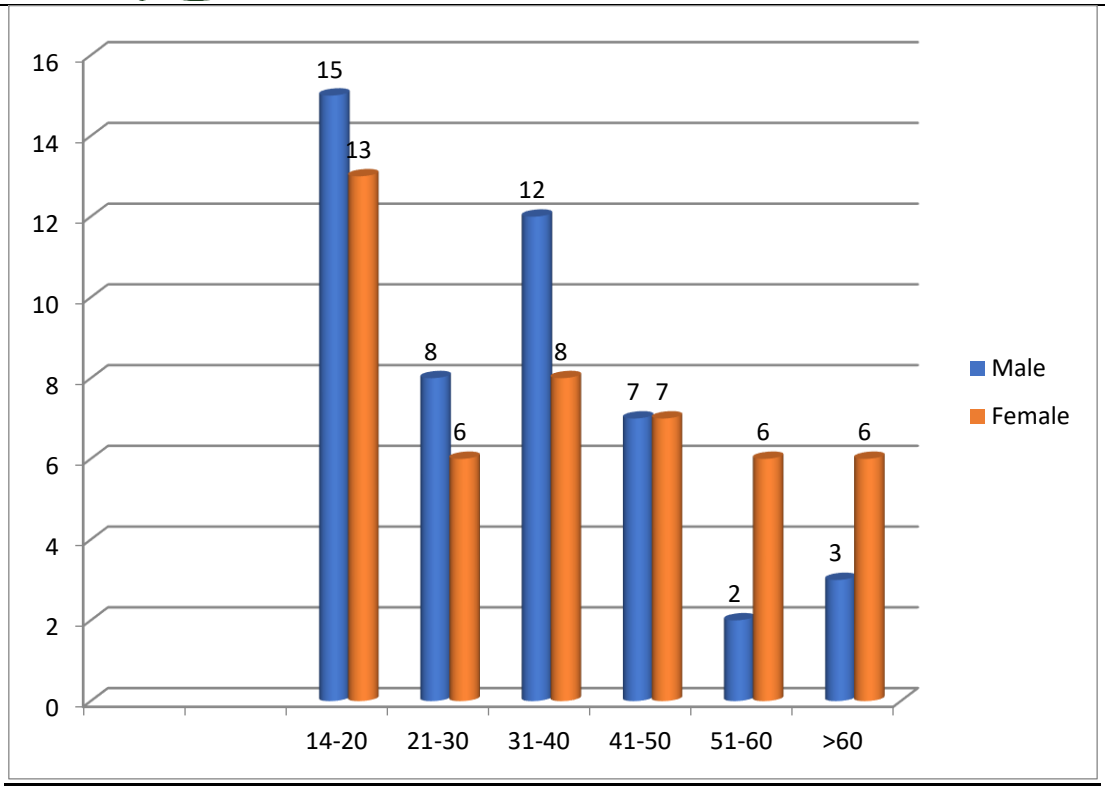
The lack of agglutination indicates a CRP concentration lower than 0.6 mg/dL. in the sample.
The data will be recorded in the predesigned proforma and then It will be entered in the MS excel and eventually it will be analysed by using statistical software -SPSS version 23. Association of qualitative data will be tested by chi square test and fischer exact test, Student t test will be applied in quantitative data. A p value < 0.05 will be considered significant.

Observation And Results

-Out of the total 93 study participants, 47(50.5) were males and 46(49.5%) are Females.

- most of the patients were of young adults <50 yr of age group. 8 patients were in the group of 51-60, 9 patients were elderly adults >60 yr age group.

GRAPH NO.1
Distribution of the participants according to age group



PREVALENCE OF POSITIVE CLINICAL PRESENTATION

TABLE NO. 1

CLINICAL PROFILE - SIGN AND SYMPTOMS		
CLINICAL PRESENTATION	**N**	**(%)**
Fever	86	93%
Headache	45	48%
Neck pain	45	48%
Vomiting	86	93%
Focal neurological deficit	21	22%
Cranial Nerve Palsy	5	5%
Blurring of vision/photophobia	5	5%
Coordination and gait	16	17%
Seizures	16	17%
Dysphagia	6	6.5%
Altered mental status	58	62.4%
Loss of Consciousness	7	7.5%
Behavioral disturbance	71	76.3%
Abnormal reflexes	6	65%
Kernig sign	76	81.8%
Brudzinski sign	30	32.5%

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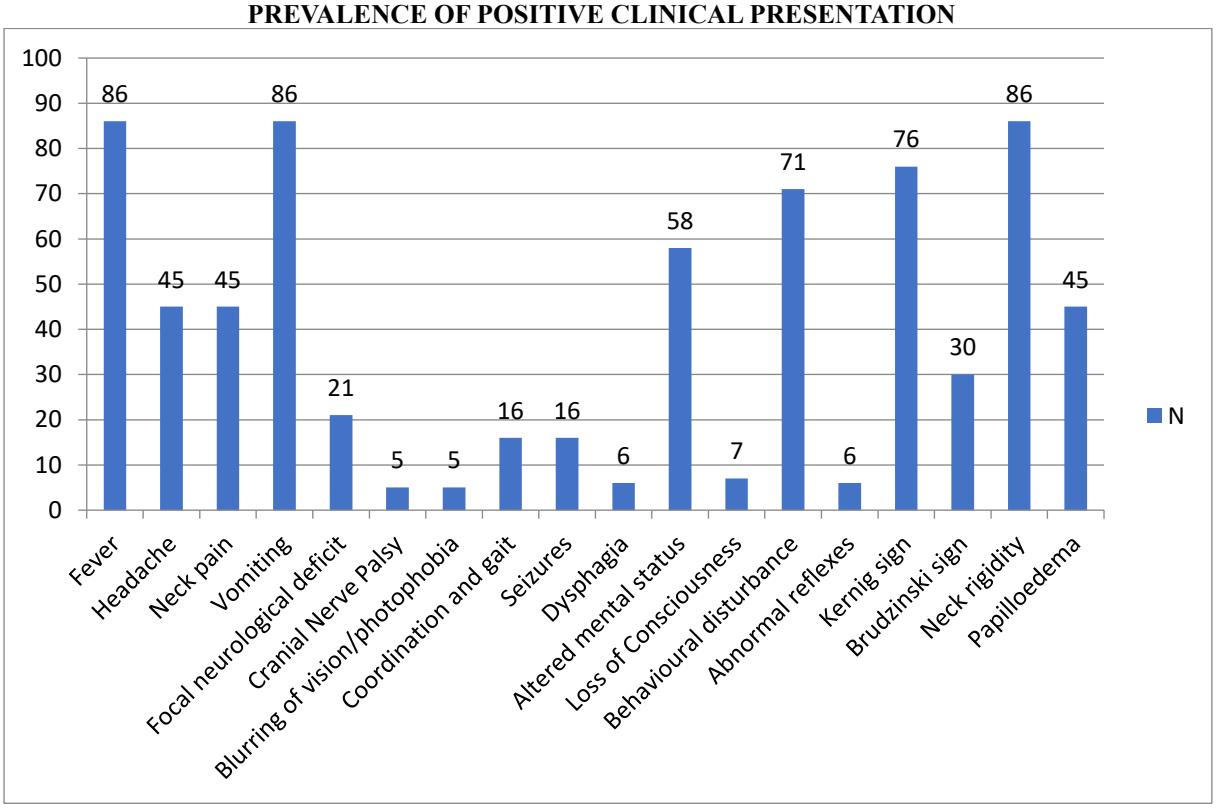
Neck rigidity	86	92.5%
Papilledema	45	48.4%

-Among the 93 patients with meningo-encephalitis in this study, the common initial presenting symptoms were fever (89%) and Vomiting (89%) > altered sensorium > headache and neck pain and stiffness> Focal neurological deficit> seizure. Fever was the most common initial presenting symptom. 86 patients (92.5%) had fever and headache (92.5%).

Headache was associated with vomiting in some of the patients. 45 patients had both fever and headache. 58 patients had altered sensorium in the course of illness, varying from drowsiness to deep coma. Only 45 patients had all the three triad – headache, fever and altered sensorium.

GRAPH NO. 2
PREVALENCE OF POSITIVE CLINICAL PRESENTATION



-16 patients had seizures during the course of illness. 5 patients had generalized tonic clonic seizures. 11 patients had focal motor seizures.

TABLE NO. 2A
DISTRIBUTION OF THE PARTICIPANTS ON THE BASIS OF ETIOLOGY

	CSF analysis					
	Bacterial M		**Viral M**		**Tubercular M**	
Sex	N (31)	%	N (25)	%	N (37)	%
Male	13	41.94%	15	60.00%	19	51.35%
Female	18	58.06%	10	40.00%	18	48.65%

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Total	31	100%	25	100%	37	100%

TABLE NO. 2B
DISTRIBUTION OF THE PARTICIPANTS AS PER AGE GROUP AND ETIOLOGY

	CSF analysis					
	Bacterial M		**Viral M**		**Tubercular M**	
Age Group	N	%	N	%	N	%
15-20	8	25.81%	10	40.00%	10	27.03%
21-30	8	25.81%	3	12.00%	4	10.81%
31-40	5	16.13%	7	28.00%	7	18.92%
41-50	3	9.68%	2	8.00%	9	24.32%
51-60	3	9.68%	2	8.00%	3	8.11%
61-70	3	9.68%	1	4.00%	3	8.11%
>70	1	3.23%	0	0.00%	1	2.70%
Total	31	100%	25	100%	37	100%

-Among 93 patients, 37 patients were diagnosed as Tuberculous meningitis. 31 patients were diagnosed as pyogenic meningitis; 25 patients were diagnosed as viral meningoencephalitis. My study also has male and younger predominance and Tubercular meningitis was the most common cause found which was followed by Bacterial meningitis and then Viral meningitis.

TABLE NO. 3A
DISTRIBUTION OF THE PARTICIPANTS BASED ON SERUM C-REACTIVE PROTEIN LEVEL AND ETIOLOGY

	CSF analysis					
	Bacterial M		**Viral M**		**Tubercular M**	
Serum CRP (mg/l)	N	%	N	%	N	%
<6	3	9.68%	19	76.00%	0	0.00%
6-12	0	0.00%	3	12.00%	3	8.11%
12-24	2	6.45%	2	8.00%	15	40.54%
24-48	7	22.58%	0	0.00%	17	45.95%
>48	19	61.29%	1	4.00%	2	5.41%
Total	31	100%	25	100%	37	100%

TABLE NO. 3B
CO-RELATION OF S-CRP WITH BACTERIAL MENINGITIS CASES

	CSF analysis	
	Bacterial M	
Serum CRP (mg/l)	N	%
<6	3	9.68%
6-12	0	0.00%
12-24	2	6.45%
24-48	7	22.58%

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>48	19	61.29%
Total	31	100%

-In my study out of 93 patient, 31 patient was found as bacterial meningitis which had s-crp value mostly ranging between >24 mg/l, out of them 19 patient had s-crp value >48 mg/l (61.29%). Most of them had poor prognosis and presented with altered sensorium and high grade fever and other focal neurological deficit and had radiological finding in the form of leptomeningeal enhancement and hydrocephalus followed by infarct in 3 cases. These 3 patients even died after few days of admission despite of giving empirical treatment.

TABLE NO. 4
CO-RELATION OF S-CRP WITH TUBERCULAR MENINGITIS CASES

Serum CRP (mg/l)	**Tubercular M**	
	N	%
<6	0	0.00%
6-12	3	8.11%
12-24	15	40.54%
24-48	17	45.95%
>48	2	5.41%
Total	37	100%

In case of tubercular meningitis, out of total 93 patient, 37 patient were diagnosed on the basis of csf analysis, clinical finding, radiological evidence and biochemical parameter with s-crp as tubercular meningitis. most of the case out of 37 had s-crp value between intermediate range (12-48) mg/l and 2 patients had range between >48 mg/l which had miliary tuberculosis. These 2 patients had poor prognosis as well and presented with altered sensorium and high-grade fever with other focal neurological deficit and had radiological finding in the form of hydrocephalus with multiple infarcts. 3 patients had crp value between (12-48) were presented with seizure and headache and had infective granuloma as positive radiological finding.

TABLE NO. 5
CO-RELATION OF S-CRP WITH VIRAL MENINGITIS CASES

	Viral M	
Serum CRP (mg/l)	N	%
<6	19	76.00%
6-12	3	12.00%
12-24	2	8.00%
24-48	0	0.00%
>48	1	4.00%
Total	25	100%

-In case of viral meningitis, out of total 93 patient, 25 patient were diagnosed on the basis of csf analysis, clinical finding, radiological evidence and biochemical parameter with s-crp as viral meningitis. most of the case out of 25 had s-crp value range <6mg/l (19 patients) followed by 3 patient had range between 6-12 mg/l followed by 2 patient had range between 12-24 mg/l and 1 patient exceptionally had s-crp more than 48 mg/l who had sepsis also.

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Discussion

This is a prospective observational, single center study done in Department of medicine NSCB medical college hospital Jabalpur in 93 patients of acute meningoencephalitis cases: 1st March.2020 to 31 August 2021. The main aim of this study is 'To study serum c-reactive protein levels in differentiating bacterial meningitis from viral meningitis'' after taking ethical clearance from Institutional Ethics Committee.

The mean age of the study participants was 35.37 years with maximum study participants i.e. 14 to 50 years of age and the most of the patient were male and young adults which is similar to the findings found in **The Tamil nadu Dr. MGR Medical University (prospective observational study) done in June 2014 – 2015**[21]**.**

In our present study on the basis of Etiology Tubercular Meningitis was found most common over all cause, which was followed by Bacterial and viral Meningitis which is similar to the findings. found in **The Tamil nadu Dr. MGR Medical University (prospective observational study) done in June 2014 – 2015**[21]**.**

(Table No.5) Among 93 patients, 37 patients were diagnosed as Tuberculous meningitis. 31 patients were diagnosed as pyogenic meningitis; 25 patients were diagnosed as viral meningoencephalitis. Thus, in comparison to the study done **Tamil Nadu Dr. M.G.R Medical University, Chennai, and in the journal of the royal 2019 where a prospective study was done in the south Indian tertiary care center,**[21] my study also has male and young predominance and Tubercular meningitis was the most common cause found which was followed by Bacterial meningitis and then Viral meningitis.

In case of clinical of profile Among the 93 patients with meningo-encephalitis in this study, the common initial presenting symptoms were fever (89%) and Vomiting (89%) > altered sensorium > headache and neck pain and stiffness> Focal neurological deficit> seizure. Fever was the most common initial presenting symptom. 86 patients (92.5%) had fever and headache (92.5%).

Headache was associated with vomiting in some of the patients. 45 patients had both fever and headache. 58 patients had altered sensorium in the course of illness, varying from drowsiness to deep coma. Only 45 patients had all the three triad – headache, fever and altered sensorium. The similar finding was also found **Tamil Nadu Dr. M.G.R Medical University, Chennai, and in the journal of the royal 2019 where a prospective study was done in the south Indian tertiary care center.**[21]

(Table no. 7) showing positive MRI and CT findings also added major contribution in differentiating the type of meningitis as well as prognosis of the disease. The most common radiological finding noticed in the study was vasculitic infarct followed by hydrocephalus followed by meningeal enhancement, granuloma and the other findings including (Thrombosis, Sinusitis, Icsol, Gliosis). Though they are not useful in the usual viral meningitis but may help to exclude other diagnosis. These Imaging is particularly helpful in later stage of TBM which shows basal enhancement and hydrocephalus. The similar findings were also noticed in the study done in Tamil Nadu Dr. M.G.R Medical University, Chennai, and in the journal of the royal 2019 where a prospective study was done in the south Indian tertiary care center. [21] and Bhargava, S Gupta, AK tandon's study (Hydrocephalus caused by tuberculous meningitis: clinical picture, CT findings and results of shunt surgery) and a study done by K. Fatema 2020, by K H Chan 2005 (TBM – CT study 1992)

In our present study on the basis of Etiology Tubercular Meningitis was found most common over all cause, which was followed by Bacterial and viral Meningitis.

In case of bacterial meningitis In my study out of 93 patients, 31 patient was found as bacterial meningitis which had s-crp value mostly ranging between >24 mg/l, out of them 19 patient had s-crp value >48 mg/l (61.29%). Most of them had poor prognosis and presented with altered sensorium and high-grade fever and other focal neurological deficit and had radiological finding in the form of leptomeningeal enhancement and hydrocephalus followed by infarct in 3 cases. These 3 patients even died after few days of admission despite of giving empirical treatment. This shows Bacterial etiology is associated with high serum CRP level in comparison to viral meningitis, where out of 25 cases of viral meningitis 19 patient had significantly CRP value < 6 mg/l and 3 patients had between 6 – 12 mg/l which concludes that serum CRP level estimation can we very helpful in differentiating viral meningitis from bacterial.

Though in Tubercular meningitis most of the patient had serum CRP level in intermediate range except two patient who had serum CRP level more than 48 mg/l. These findings also found similar in the study of Konatham Rambabu Kathyayani M K M (The significance of serum c- reactive protein estimation in acute

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meningitis in adults), *Devanayagam* et *al* (1993) (Clinical epidemiology unit, Madras Medical college, Brown et al. (1978), D Diculencu [22], E Miftode, T Turcu, D Buiuc (The value of C-reactive protein for the differentiation of bacterial meningitis from viral meningitis), José Diego Santotoribio , Juan Francisco Cuadros-Muñoz , Natalia García-Casares (Comparison of C Reactive Protein and Procalcitonin Levels in Cerebrospinal Fluid and Serum to Differentiate Bacterial from Viral Meningitis), Suchat Sirijaichingkul et al. (JMED association Thai 2005 sep.) also concluded that S-CRP can help in differentiating between bacterial and Aseptic Meningitis , Frizzo et al. Quad Sclavo Diagn. 1987, Lars-Olof Hansson , Gudmundur Axelsson , Tommy Linne ,Elisabeth Aurelius & Lars Lindquist Pages 625-630 Published online: 08 Jul 2009 (Serum C-reactive Protein in the Differential Diagnosis of Acute Meningitis), R Mary et al. Ann Biol Clin (Paris) 2003 [Acute meningitidis, acute phase proteins and procalcitonin], J Sutinen et al. Infectious disease (Etiology of central nervous system infections in the Philippines and the role of serum C-reactive protein in excluding acute bacterial meningitis (1998 to 1999)

Summary & Conclusion

In this study, most of the patients with meningoencephalitis were males and young adults. Surprisingly, Tuberculous meningitis was the most common overall cause in this study. This observation is in contrast to the Western literature. Viral etiology in the most common one in western population. Both viral meningo encephalitis and pyogenic meningitis constituted most of the cases of acute Meningoencephalitis. Tuberculous meningitis was the most common cause in patient with sub-acute meningitis. Diagnosis of tuberculous meningitis was challenging; clinical presentation, CSF studies and brain imaging features helped to make a diagnosis of tuberculous meningitis. Estimation of C-reactive protein in serum is the cheapest, sensitive and specific test to differentiate bacterial from viral infections. It is a simple qualitative as well as quantitative test and can be done as a bed side investigation. With serum C-reactive protein, a definite etiological diagnosis can be made rapidly at the time of admission itself. A serum CRP level of less than 6 mg/l with clinical signs of meningeal infection is a definite indicator of viral meningitis. A serum CRP level of more than 48 mg/l with clinical signs of meningeal infection is a definite indication of bacterial meningitis. Preadmission treatment with steroids causes a fall in CRP levels in bacterial meningitis. Serum CRP has 68% predictive value in adults. The rapid differentiation facilitates an early, accurate and appropriate therapy thereby reducing the mortality and morbidity rates, the overall cost of the treatment and the duration of hospitalization. Serum CRP can be used as the best and most sensitive bedside prognostic indicator of bacterial infections. Meningeal infections have a definite male predominance. Altered level of consciousness at the time of admission is associated with bad prognosis and high case fatality rate (28%). Among the 93 patient with meningoencephalitis in this study, the common initial presenting symptoms were fever (89%) and Vomiting (89%) > altered sensorium> headache and neck pain and stiffness>Focal neurological deficit> seizure. Fever was the most common initial presenting symptom. 86 patients (92.5%) had fever and headache (92.5%).

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