

Research Article

Role of C- reactive proteins in cerebro-spinal fluid in differentiating pyogenic from nonpyogenic meningitis

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ABSTRACT

Background: In developing countries like India meningitis is major cause of morbidity and mortality because of delay in proper diagnosis and consequently delay in proper treatment. For the appropriate treatment of meningitis, differentiation of various types of meningitis is essential. The diagnosis of meningitis in a govt. hospitals is usually made by examination of CSF, Gram staining, AFB, CSF culture and associated clinical findings. All these laboratory techniques have their limitations. So we need a diagnostic test which is rapid, reliable and cost effective. In the present study we used CRP levels in CSF sample to differentiate pyogenic from non-pyogenic meningitis and to establish a cut off level for CRP.

Methods: The study is a hospital based prospective study carried out in the setting of department of pathology, microbiology, casualty and various wards of Netaji Subash Chandra Bose Medical College Jabalpur (M.P) India during November 2014 to October 2015. During study period we took samples (Blood and CSF) from 138 cases of suspected meningitis.

Results: Value of CRP was 32.50645 ± 2.032886 in PM cases, 1.543373 ± 0.195181 in TBM cases and VM cases value were 2.420833 ± 0.357502 . Statistically significantly higher value was observed with pyogenic meningitis cases compared to TBM and VM cases. ($p < 0.001$). At 10 U/L cut off value, sensitivity and specificity of CSF- CRP was 93.5% and 94.4% respectively.

Conclusions: On the basis of present study we concluded that CRP can be used as a rapid confirmatory test since elevated CRP are highly suggestive of pyogenic meningitis.

Keywords: C-reactive protein, Pyogenic meningitis, tubercular meningitis, viral meningitis, CSF, meningitis

INTRODUCTION

The annual incidence of bacterial meningitis is 2.5 cases/100,000 population in the united states.¹ More than 2000 deaths due to bacterial meningitis are reported annually in the United States. In developing countries like India meningitis is major cause of morbidity and mortality because of delay in proper diagnosis and consequently delay in proper treatment. For the appropriate treatment of meningitis, differentiation of various types of meningitis is essential. The diagnosis of

meningitis in a govt hospitals is usually made by examination of CSF, Gram staining, AFB, CSF culture and associated clinical findings. All these laboratory techniques have their limitation.

So we need a diagnostic test which is rapid, reliable and cost effective. In this context CPR and ADA of CSF can be used as rapid tests for the diagnosis of meningitis. The disease is more common with higher morbidity and mortality in the developing countries like India, other Asian and African countries. The prognosis of bacterial

meningitis is critically dependent on an early diagnosis and implementation of prompt treatment. The initial treatment of meningitis is mostly presumptive. The definitive diagnosis, however difficult, is often established when the therapeutic management has already been initiated.

The use of biological markers, especially lymphokines, acute-phase proteins, has been proposed to facilitate the accuracy of the early initial diagnosis. Now a day, quantitative C-reactive protein (CRP) measurement is the widely used inflammatory marker in emergency with aim to differentiate bacterial from non-bacterial infections, but CRP values must be interpreted in relation to the clinical, biochemical and microscopic context.

CRP is an acute-phase protein produce exclusively in the liver.² Serum concentration of CRP increases significantly in cases of both infectious and non-infectious inflammation, tissue damage and necrosis and in the presence of malignant conditions.

Usefulness of CSF CRP in differentiating Pyogenic from nonpyogenic meningitis has been documented in several studies.³⁻⁷ Hence in the present study we used CRP levels in CSF sample to differentiate pyogenic from non-pyogenic meningitis and to establish a cut off level for CRP.

METHODS

The study is a hospital based prospective study carried out in Department of Pathology, NSCB Medical college Jabalpur during period of one year Nov 2014 to Oct 2015.

CSF and blood samples were obtained from patients who presented with sign and symptoms of suspected meningitis. Instruction and cutoff values regarding CRP test were followed as per guideline provided by Biosystems reagents and instruments. During study period we took samples of 138 patients as case of suspected meningitis. Clinical criteria for diagnosis of meningitis- Presence of one/more of following mentioned clinical finding at time of hospital admission -

- Triad of fever , headadhe, nuchal rigidity
- Altered mental status
- Nausea, vomiting and photophobia
- Seizures
- Signs of meningeal irritation

Criteria for diagnosing different types of Meningitis.⁸

Group 1: included cases of tubercular meningitis based on:

Clinical features- usually insidious in onset, may be associated with tuberculosis of other organs, signs of meningeal irritation.

CSF analysis- Pleocytosis of >10 cells/mm³ predominantly lymphocytes, proteins >45mg/dl, Glucose < 40 mg/dl or less than 40% of blood glucose concentration, Ziehl Neilsen may be positive for AFB, Neuroimaging: Meningeal enhancement, basal eudates and /or tuberculoma.

Group 2: Included case of pyogenic meningitis based on clinical features- usually acute in onset, may be associated with sinusitis, otitis media and signs of meningeal irritation.

CSF analysis- Pleocytosis of >250 cells/cumm predominantly neutrophils, proteins > 45 mg/dl, Glucose <40mg/dl or less than 40% of the blood glucose concentration, Gram stains and culture, Neuroimaging- Diffuse meningeal enhancement, abscess or parameningeal focus.

Group 3: Included case of viral meningitis based on:

Clinical presentation: usually acute in onset with signs of meningeal irritation.

CSF analysis- Lymphocytic pleocytosis of > 25 cells/cumm, Proteins >45mg/dl, Glucose- 45-80mg/dl, Neuroimaging- diffuse meningeal enhancement.

Inclusion criteria

Patient of all age group with suspected sign, symptoms and clinical features suggestive of meningitis.

Exclusion criteria

Patient already on treatment of meningitis. A patients with acute infection at sites other than CNS. Patient in whom lumbar puncture is contraindicated. Associated sever hepatic dysfunction. Females on oral contraceptives and intrauterine device. Sever dyslipidemia and patients on steroid treatment.

CRP testing: Quantitative latex agglutination test was used for detection of CRP. CRP causes agglutination of latex particles coated with anti-human CRP. The agglutination of the latex particles is proportional to the CRP concentration and is measured by turbidimetry (56).

RESULT

In the present study out of 138 cases there were 31 cases of pyogenic meningitis, 107 cases of Non-pyogenic meningitis which includes 83 tubercular and 24 cases of viral meningitis.

The mean age for viral meningitis was 20.17±16.99, for Tubercular meningitis was 26.96±19.49 and mean age for pyogenic meningitis was 19.76±21.55. Statistically no significant difference was seen.

(p>0.05) There were 61.3% male and 38.7% females in pyogenic meningitis group, 73.5% male and 26.5% females in tubercular meningitis and 62.5% male and

37.5% females in VM. Overall male case were more in number compared to female in our study, however there were no statistically significant difference seen. (p>0.05).

Table 1: CRP values in meningitis cases.

	TBM (n=83)	PM (n=31)	VM (n=24)
CRP (mg/dl)	1.543373±0.195181	32.50645±2.032886	2.420833±0.357502

Table depicts the CRP values in meningitis cases. Value of CRP were 32.50645±2.032886 in pyogenic meningitis cases, 1.543373±0.195181 in tubercular meningitis cases, and viral meningitis cases value were 2.420833±0.357502. Statistically significantly higher value was observed with pyogenic meningitis cases compared to TBM and VM cases (p<0.001).

The cut-off for CSF-CRP was taken as 10mg/dl as per the literature of the kit manufacturer (Biosystem reagent). In the present study 29 out of 31 cases of pyogenic meningitis had CSF-CRP levels >10 mg/dl and only 2 cases had CSF-CRP <10 mg/dl. There were 83 cases of tubercular meningitis out of which only 6 cases had CSF-CRP >10 mg/dl rest all had values <10 mg/dl.

In viral meningitis cases (24) all showed CSF-CRP <10 mg/dl. At 10mg/dl cut-off value sensitivity and specificity of CSF-CRP for diagnosis of pyogenic meningitis was 93.5% and 94.4% respectively while PPV, NPV and diagnostic accuracy were 82.9, 98.1 and 94.2 respectively.

DISCUSSION

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 compare to non-pyogenic meningitis and hence aid in the differential diagnosis and management of meningitis.⁹⁻¹²

In our study, the mean CRP in CSF of patients with pyogenic meningitis, tubercular meningitis and viral meningitis were; 32.50±2.03 mg/dl, 1.54±0.19mg/dl and 2.42±0.35 respectively. The finding of our study is that CSF-CRP is significantly higher in pyogenic meningitis compare to non-pyogenic meningitis.

The cut-off value for CSF-CRP was taken as per the guidelines provided by manufacturer of the CRP reagent (Biosystem). This result remain statistically significant with p<0.001. The sensitivity and specificity of the test was 93.5% and 94.4% respectively.

A recent met-analysis by Gerdes LU et al and Sutinen J 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 compare to tubercular meningitis.¹³⁻¹⁵

Authors concluded that the estimation of CRP in the differential of meningitis can be made to give a preliminary diagnosis of meningitis. Another study conducted by Hemavani V et al evaluated the role of CSF-CRP in differentiation of meningitis. The study included 499 CSF samples from cases of viral, pyogenic, tubercular and fungal meningitis and 580 normal CSF samples.¹¹

CRP positive by qualitative latex agglutination test was seen in 73.3% of CSF samples from partially treated pyogenic meningitis and 92.0% among Pyogenic meningitis cases.

The study concludes that CSF CRP determination can be of value to differentiate pyogenic versus other microbial meningitis etiology. However, it cannot differentiate between tubercular, fungal and viral meningitis. Study by Tankhiwale SS et al on 75 case of clinically, biochemically and microscopically diagnosed cases of pyogenic meningitis.¹⁵

A total of 66 patients showed raised CRP levels in either in serum of CSF while only 27 yielded bacterial growth in culture. The difference was statistically significant. Hence the author concluded that estimation of CRP in CSF and serum help as an early marker for rapid diagnosis of pyogenic meningitis. Study by Kerner A et al shows association of hepatic dysfunction dyslipidemia in meningitis patients, and study by Rooijen VM et al shows association of oral contraceptives in females and patient on steroids in meningitis cases, so these patients were not included in our study, because these factors independently affects CRP levels.^{16,17}

CONCLUSION

On the basis of present study we concluded that CRP can be used as a rapid confirmatory test since elevated CRP are highly suggestive of pyogenic meningitis.

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