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RESEARCH ARTICLE

Significance of c reactive protein (CRP) in meningitis- a prospective observational study

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ABSTRACT

Introduction: Meningitis, which is potentially a serious problem among all age groups. This may progress to severe and permanent neurological deficits and even death too. Various parameters are used to diagnose and differentiate among meningitis. C reactive protein may be one of them.

Aims and objectives: To establish the significance of CSF as well as serum CRP in diagnosing and differentiating pyogenic and tubercular meningitis.

Method: Prospective observational study conducted in Govt. medical college, Kota. Age and sex matched 100 patients (40 0f pyogenic meningitis, 40 of tubercular meningitis & 20 as control) were included. Serum and CSF CRP was estimated.

Results: The incidence of tubercular and bacterial meningitis was maximum in adult age group (56% and 52% respectively). CT Scan of head showed abnormalities in 40% cases of tubercular meningitis as compared to 20% cases of pyogenic meningitis. In adults sensitivity of Serum CRP in pyogenic meningitis is 100% and in tubercular meningitis 93.75%. Specificity of Serum CRP was 64.28% in both groups. Sensitivity of CSF-CRP in pyogenic meningitis is 17.65% and tubercular meningitis is 18.75%. Specificity in both the conditions is 92.86%. Predictive value of positive CSF-CRP in both groups is 75%.

Serum CRP was statistically significant in both pyogenic ($p<0.004$) and tubercular meningitis ($p<0.002$) in comparison with control group. CSF-CRP was not significantly raised as compared to controls.

Conclusion: There is a significant correlation between CSF-CRP and serum CRP in pyogenic meningitis in pediatric age group. In adult age group, no significant correlation between serum and CSF-CRP levels in pyogenic meningitis cases was found. Hence restricting its role in the diagnosis in adults population. In tubercular meningitis both serum and CSF-CRP levels estimation could not achieve statistical significance in both the age groups.

Key words: C reactive protein; Pyogenic meningitis; Tubercular meningitis

INTRODUCTION:

Acute infections of nervous system are among the most important problems in medicine because early recognition, efficient decision making and rapid institution of therapy can be life saving. These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, encephalitis, focal infections as brain abscess, subdural empyema and infectious thrombophlebitis. Meningitis remains a major public health problem worldwide both among children and adults. Neurological outcome and survival depends largely on the damage to CNS prior to effective antibacterial treatment. The epidemiology of meningitis has changed over last two decades with the use of vaccines and emergence of antibiotic resistance. In the adults most common organism causing pyogenic meningitis include Streptococcus pneumonia, Neisseria meningitides, Haemophilus influenzae, Listeria and Staphylococcus. Tubercular meningitis is a subacute and chronic inflammatory congestion of meninges with greater prevalence in developing world. CSF analysis comprising of sugar, proteins and cell analysis has been used as a traditional and reliable means of diagnosis and differentiation. Recently various acute phase markers are gaining popularity for differentiating pyogenic form tubercular meningitis.

C reactive protein has been an established marker of acute phase reaction in various pathological conditions. C reactive protein unlike IgG recognizes altered self and foreign molecules based on pattern recognition. CRP

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gene is located on first chromosomes (1q21-q23) encoding for a 224 residue protein with a molar mass of 25106 Da and configuration known as pentraxins. A number of early prospective studies have tried to define an association between C reactive protein and type of meningitis. CRP is synthesized by hepatocyte.[1] It is normally present as a trace constituents of plasma with median value is less than 3µg/ml (90% health adults).[2] CRP begins to rise following inflammatory stimulus within 4-6 hours, peaks at 36-50 hours and allowing to normal 3-7 days after the stimulus is withdrawn. The half-life estimated approximately 4-7 hours.[3] A number of functions have been ascribed to CRP including initiation of opsonisation, phagocytosis and activation of compliment, neutrophils, macrophage and monocytes. Collectively these properties imply an important role for CRP in the recognition of microbial organisms and as an immunomodulator in host defence.[3] Advantages of measuring CRP include easy measurement, rapid response, short half life, large incremental change and catabolism not being affected by type of inflammation.[3] Several methods have been mentioned for measurement of CRP including latex agglutination, laser nephelometry, Radioimmunoassay, etc. CSF CRP concentration is 7 fold lower than that of serum. This difference is explained by direct hepatic release of CRP into plasma which then undergoes ultrafiltration into the CSF. But the evidence shows that this may occur only in inflamed meninges. Still some authors recommend CSF-CRP as important tool in differential diagnosis of meningitis.[3] Serial estimations are useful in monitoring the response.[4] CSF-CRP levels are higher in pyogenic meningitis then tubercular meningitis. This was proposed to be due to greater destruction by bacteria than tubercular bacilli and extracellular life cycle of bacteria.[5] This study also attempts to find out the relation of Serum C reactive protein and CSF C reactive protein with different types of meningitis and tries to find its predictive value.

MATERIAL AND METHODS:

The study was conducted at Govt. Medical College, Kota and Associated Group of Hospitals. The study population comprised of indoor patients admitted with a diagnosis of meningitis in Medical and Neurological wards. We included 40 patients of pyogenic meningitis, 40 patients of tubercular meningitis and 20 controlled patients. We tried to include all age groups and both sexes.

For pyogenic meningitis:

Inclusion criteria:

1. Clinical presentation suggestive of pyogenic meningitis (such as fever, headache, stiffness of neck, with or without convulsion and altered sensorium.

2. CSF finding suggestive of Pyogenic meningitis [such as Pleocytosis (range 250-100,00/mm^3, 85-90% neutrophils), Increased proteins (range 100-500 mg/dl), decreased sugar <40 mg/dl, <40% of blood glucose level).

Exclusion criteria:

1. Equivocal cerebrospinal fluid findings,
2. CT head showing cerebral abscess, infarct, subdural effusion, hematoma, subdural empyema, meningismus but no CSF correlation/substantiation.

For Tuberculous meningitis:

Inclusion criteria:

1. Clinical presentation suggestive of tuberculous meningitis [fever and headache (for >14 days), vomiting, altered sensorium or focal neurological deficit.]

2. CSF finding suggestive of tuberculous meningitis [Pleocytosis (>20 cells, >60% Lymphocytes), Increased proteins (>100mg/dl), low sugar (<60% of corresponding blood sugar), Indian ink studies and microscopy for malignant cells should be negative.

Exclusion criteria:

1. Other etiologies of chronic meningitis like fungal meningitis and carcinomatous meningitis, any primary malignancy found elsewhere even if CSF does not show malignant cells,
2. Equivocal CSF findings, hyper acute/rapid response (within hours) to therapy,
3. CT head showing Subdural Hematoma, large abscess (CT head showing exudates, vascular infarct, and hydrocephalus will be included).

A detailed clinical history examination review of medical records was done. Lab investigations included haemogram, ESR, Biochemistry, Chest X-ray. Special investigations were analysis of serum, CRP, CSF analysis including biochemistry cell count & typing, microscopy (Gram & AFB staining) culture and sensitivity and CRP estimation. CT scan was performed in all cases.

CRP estimation in serum and CSF was done by latex agglutination slide test which is a semi-quantitative method on the principle of agglutination of anti CRP antibody coated polystyrene latex particles by bacterial antigens. Visible agglutination was observed at CRP concentrations of 6mg/L or higher.

RESULTS

Most of the patients enrolled were in 15-60 years of age group. The male female ratio was 1.38:1 in study group and 1:1.22 in control group. The incidence of tubercular and bacterial meningitis was maximum in adult age group (56% and 52% respectively). The symptoms in pyogenic and tubercular meningitis patients were fever (100% vs 88%), headache (76% vs 80%), vomiting (52% vs 84%), altered sensorium (42% vs 20%), convulsions (36% vs 40%), loss of bladder & bowl control (42% vs 36%), photophobia and others.

CT scan of head showed abnormalities in 40% cases of tubercular meningitis as compared to 20% cases of pyogenic meningitis. CSF analysis was clear in control group whereas the findings in pyogenic and tubercular meningitis groups were turbidity (48% in pyogenic), cobweb in 44% of tubercular meningitis cases, raised CSF proteins (96% vs 92%), low sugar levels (76% vs 36%), CSF blood sugar ratio less than 0.04 (76 vs 56). In pyogenic meningitis group more than 80% neutrophils were seen in 100% of cases. In tubercular meningitis more than 60% lymphocytes in CSF were present in all. CSF culture for bacteria was positive in 60% cases of pyogenic meningitis with N. meningitides as most prevalent bacteria (35%). Serum CSF was positive in all case of pyogenic meningitis, 96% cases of tubercular meningitis and 40% of control group. CSF-CRP was positive in 87.5% pediatrics cases of pyogenic meningitis while it was positive in only 17.6% adult patients. CSF-CRP was positive in 22.2% pediatric cases and 18.75% adult cases of tubercular meningitis. Only 1 of the control group was positive for CSF-CRP.

In pediatric population, the sensitivity of Serum CRP in both meningitis groups is 100% and specificity 16.67%. Predictive value of positive Serum CRP in pyogenic meningitis is 61.5% and in tubercular meningitis 64.28%. Sensitivity of CSF-CRP in pyogenic meningitis is 87.5% and tubercular meningitis is 28.5%. Specificity in both the conditions is 100%. Predictive value of positive CSF-CRP in both groups is 100%.

In adult population, the sensitivity of Serum CRP in pyogenic meningitis is 100% and in tubercular meningitis 93.75%. Specificity of Serum CRP was 64.28% in both groups. Predictive value of positive Serum CRP in pyogenic meningitis is 77.27% and in tubercular meningitis 75%. Sensitivity of CSF-CRP in pyogenic meningitis is 17.65% and tubercular meningitis is 18.75%. Specificity in both the conditions is 92.86%. Predictive value of positive CSF-CRP in both groups is 75%.

In adult age group Serum CRP was statistically significant in both pyogenic ($p<0.004$) and tubercular meningitis ($p<0.002$) in comparison with control group. In pediatric group Serum CRP levels were not significant in both the groups. In pediatric group CSF-CRP was statistically significant ($p<0.006$) in pyogenic meningitis cases as compared to controls. In adult group CSF-CRP was not significantly raised as compared to controls. CSF-CRP was not significantly elevated in tubercular meningitis group both pediatric and adults when compared to controls.

Table 1: Clinical presentation in both groups

Symptoms	Pyogenic meningitis (%)	Tubercular meningitis (%)
Fever	100	80
Headache	76	80
Vomiting	52	84
Altered Sensorium	42	20
Convulsions	36	40
Loss of bowel bladder control	42	36

Table 2: CSF study in pyogenic and tubercular meningitis

CSF finding	Pyogenic meningitis	Tubercular meningitis
Raised protein	96 %	92%
Low sugar	76%	36%
Cobweb	0	44%
Predominant cells	neutrophils	Lymphocytes

Table 3: Statistical comparison of CRP in meningitis (Adults)

	Pyogenic meningitis	Tubercular meningitis
Sensitivity of serum CRP	100%	93.75%
Sensitivity of CSF CRP	17.65%	18.75%
Specificity of serum CRP	64.2%	64.2%
Specificity of CSF CRP	92.86%	92.86%
Positive predictive Value in CSF CRP	75%	75%
Positive predictive value of serum CRP	77.27%	18.75%

Table 4: Statistical comparison of CRP in meningitis (Children)

	Pyogenic meningitis	Tubercular meningitis
Sensitivity of serum CRP	100%	100%
Sensitivity of CSF CRP	87.5%	28.5%
Specificity of serum CRP	16.67%	16.67%
Specificity of CSF CRP	100%	100%
Positive predictive Value in CSF CRP	61.5%	64.28%
Positive predictive value of serum CRP	100%	100%

Discussion

Thus in our study, in pyogenic meningitis cases, CSF-CRP has sensitivity of 87.5%, specificity 100% and predictive value of positive test 100%. In tubercular meningitis cases CSF-CRP has sensitivity of 28.5% and specificity 100%. Prasad et al[7] reported sensitivity and specificity of CSF-CRP as 96% & 100%, Kalra et al[8] reported sensitivity and specificity as 96% and 28%. Ahmed et al[9] reported significant elevation in serum and CSF-CRP levels in patients of pyogenic meningitis whereas the levels in tubercular meningitis cases were intermediate between those of pyogenic meningitis and viral encephalitis ($p<0.001$). Concentrations of CRP in tubercular meningitis

lay between those of bacterial and viral meningitis, a finding which detracts from virtually absolute discrimination, CRP measurement allows between bacterial and viral meningitis. The reason for higher CRP values in the serum and CSF in pyogenic meningitis may be due to greater inflammatory response induced by pyogenic infections as compared to tubercular infections.

In this study, there is a significant correlation between CSF-CRP and serum CRP in pyogenic meningitis in pediatric age group. Hence it is recommended to measure serum and CSF-CRP levels as a routine test for rapid and early diagnosis of pyogenic meningitis in children. This test may have still greater importance in patients with partially treated pyogenic meningitis in pediatric age where CSF picture may not be classical. In adult age group, no significant correlation between serum and CSF-CRP levels in pyogenic meningitis cases was found. Hence restricting its role in the diagnosis in adult population. In tubercular meningitis both serum and CSF-CRP levels estimation could not achieve statistical significance in both the age groups.

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