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CLINICAL & BASIC RESEARCH

Is Cerebrospinal Fluid C-reactive Protein a Better Tool than Blood C-reactive Protein in Laboratory Diagnosis of Meningitis in Children?

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هل فحص البروتين الفعال C (CRP) في السائل الدماغي الشوكي أفضل من فحصه في الدم لتشخيص مرض السحايا في الأطفال مخبريا

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الملخص: **الهدف**: اختبار مدى كفاءة استخدام فحص البروتين الفعالC (CRP) لتشخيص الأنواع المختلفة من التهاب السحايا بهدف استخدام الفحص روتينيا. **الطريقة**: أجريت الدراسة على 140 طفل أدخلوا للعلاج في مستشفى مانيبال التعليمي في بخارى, نيبال في الفترة يوليو/ تموز 2009 إلى يونيو/ حزيران. تم التحليل التفصيلي لعينات الدم و السائل الدماغي الشوكي متضمنا فحص البروتين الفعالC (CRP) لأولئك المرضى. **النتائج**: وجد أن 31.1% لديهم سحايا صديدية (PM) و 26.2% سحايا معالجه جزئيا (PPM) و33% سحايا فيروسيه (VM) و 9.7% سحايا السل(TBM). 26.4% غير مرضي تم استخدامهم كضوابط للدراسة. تم عزل 12.5% من العينات المصابة بالزراعة الجرثوميه المخبريه للدم و 25% منها بزراعة السائل الدماغي الشوكي. كانت النتائج إيجابيه ل CRP في الدم لكل أنواع السحايا في الدراسة وكانت أعلى نسبه ايجابيه في السحايا الصديدية (53.12 ± 28.88 mg/dl), السحايا المعالجة جزئيا ولكن لم يكن الفرق معتمد إحصائيا(P = 0.08). اما مستوى CRP في السائل الدماغي الشوكي فقد كان أعلى من الأنواع الأخرى بفارق معتمد إحصائيا (P <0.001) ففي السحايا الصديدية كان المستوى, (45.75 ± 28.50 mg/dl) وفي السحايا المعالجة جزئيا (53.12 ± 28.88 mg/dl).الحساسية التحليلية والنوعية التحليلية لفحوصات CRP في الدم كانت كالآتي: 90.62%, 88.88%, 64.70%, 70% و32.40%, 30.97%, 24.52%, 26.12% ولفحوصات CRP في السائل الدماغي الشوكي هي 96.87%, 66.66%, 20.58%,10% و74.73%, 63.71%, 50.94%, 55.35% لأنواع السحايا الصديدية, السحايا معالجة جزئيا, السحايا الفيروسية, وسحايا السل بالتتابع. **الاستنتاج**: بسبب الحساسية العالية لفحوصات CRPفي الدم وفي السائل الدماغي الشوكي يمكن استخدامه لفحص السحايا البكتيرية (الصديدية والمعالجة جزئيا). لقد أظهر فحص CRP في السائل الدماغي الشوكي نتائج بنوعية تحليلية أفضل من فحص CRP في الدم ولهذا يمكن استخدامة كفحص مساند مع فحوصات السائل الدماغي الشوكي المخبريه الأخرى الكيميائية و الجرثومية لتشخيص السحايا.

مفتاح الكلمات: السحايا، البروتين الفعالC (CRP)، السائل الدماغي الشوكي.

ABSTRACT: ***Objectives:*** This study aimed to test whether C-reactive protein (CRP) measurement could differentiate between different types of meningitis and become a routine test. ***Methods:*** A prospective study included 140 children admitted to Manipal Teaching Hospital, Pokhara, Nepal, between July 2009 and June 2011. The subjects had a blood test and detailed cerebrospinal fluid (CSF) analysis, including blood and CSF CRP levels. ***Results:*** Of those admitted, 31.1% had pyogenic meningitis (PM), 26.2% partially treated meningitis (PPM), 33% viral meningitis (VM), and 9.7% tubercular meningitis (TBM), with 26.4% controls. Organisms were isolated in 12.5% of the cases by blood culture and 25% of cases through CSF culture. Blood CRP was positive in all groups, with the highest values in PM (53.12 ± 28.88 mg/dl) and PPM (47.55 ± 34.34 mg/dl); this was not statistically significant ($P = 0.08$). The CSF CRP levels were significantly higher ($P < 0.001$) in PM (45.75 ± 28.50 mg/dl) and PPM (23.11 ± 23.98 mg/dl). The sensitivity and specificity of blood CRP was 90.62%, 88.88%, 64.7%, 70% and 32.4%, 30.97%, 24.52%, 26.12% and that of CSF CRP was 96.87%, 66.66%, 20.58%, 10% and 74.73%, 63.71%, 50.94%, 55.35% for PM, PPM, VM and TBM, respectively. ***Conclusion:*** Because of its high sensitivity, both CSF CRP and blood CRP can be used to screen for bacterial meningitis (both PM and PPM). CSF CRP screening yielded results with a higher specificity than blood CRP; hence, it can be a supportive test along with CSF cytology, biochemistry, and microbiology for diagnosing meningitis.

Keywords: Meningitis; C-reactive protein; Cerebrospinal fluid.

Advances in Knowledge

- *Blood and cerebrospinal fluid (CSF) C-reactive protein (CRP) can be a simple bedside test to differentiate between different types of meningitis.*
- *Both can be especially helpful in diagnosing partially treated meningitis when patients present after being prescribed antibiotics, and the CSF picture is similar to viral meningitis.*

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Application to Patient Care:

- *Blood and CSF CRP help in the early diagnosis and appropriate treatment of different types of meningitis.*
- *Early treatment prevents the chances of having negative sequelae.*

C-reactive protein (CRP) and the acute phase inflammatory response were discovered in 1930 by Tillett *et al.*[1] Almost any inflammatory disease will cause detectable quantities of CRP to be present in serum or other body fluids closely associated with the affected tissues.[2,3] In Western countries, attention has been directed to the value of serum CRP measurement in differentiating bacterial and viral infections.[4] However, routine diagnostic use of cerebrospinal fluid (CSF) CRP in differentiating bacterial and non-bacterial meningitis has been evaluated in very few studies.[2,5] The CSF Gram stain and culture still remains the gold standard in the diagnosis of meningitis, but in patients where these results are negative, there is no definitive test for diagnosing meningitis. This is especially necessary in a set up like ours where patients come after getting various antibiotics or where facilities for doing cultures are not readily available. Death from meningitis is not uncommon and many who survive are left permanently disabled. Hence, diagnostic tests which are readily available, easy to interpret, and simple to perform are of paramount importance. The present study was designed to evaluate the diagnostic significance of CRP in CSF and blood as a rapid and simple method of diagnosing and differentiating different types of meningitis in children in a developing country like Nepal where there is a problem in isolating organisms.

Methods

This hospital-based case controlled study was conducted from July 2009 to June 2011, in the Paediatric Ward of Manipal Teaching Hospital in Pokhara, Nepal. This is the only tertiary care hospital in the western region of the country and has a 75-bed paediatric ward. Therefore, mostly very sick patients with a diagnostic dilemma who are not responding to simple management are referred to this hospital; hence, most patients come after receiving a course of antibiotics.

Before the commencement of the study, ethical approval was obtained from the Ethical Committee of the Hospital and informed consent from the parents/guardians. A separate proforma, which included data about clinical features and laboratory results, was completed for each case.

A lumbar puncture was done on all children aged 1 month to 15 years who were included in the study. Blood and CSF samples were also sent for CRP assay by latex agglutination test. The volume of CSF used for CRP analysis was 500 µl (~0.5 ml) = 8 drops, and was assessed using a series of diagnostic kits/reagents which included biochemistry, immunology, and serology rapid tests from RFCL Limited (Ranbaxy Fine Chemicals Ltd., Delhi, India). Other laboratory investigations included an assessment of blood sugar, and a blood culture. A CSF CRP titre of 4 mg/L and a blood CRP of 6 mg/L were considered positive in this study.[1,6] These values were the cut-off values and matched with their reference value. A CSF Gram stain and culture were performed as gold standard testing. In cases where the staining results were negative, CSF cytology, and glucose and protein levels were considered. CSF and serum CRP were then evaluated against this gold standard. All 140 patients were divided into 5 groups based on clinical and CSF cytochemistry.[7]

Group 1, with pyogenic meningitis (PM), was defined by a CSF leukocyte count of 100–10,000/mm^3 with polymorphonuclear neutrophils (PMNs) of >50%, a CSF glucose level <2/3 blood sugar level, and a CSF protein level of 100–500 mg/dl. Group 2, with partially treated meningitis (PPM), was defined as those who had already received oral or intravenous antibiotics before CSF analysis. These patients had a CSF leukocyte count of 5–10,000/mm^3 with PMNs or lymphocytes predominating, protein levels of 100–500mg/dl, and normal or decreased glucose levels. Group 3, with viral meningitis (VM), was defined as those with a CSF pleocytosis of <100/mm^3 with lymphocyte predominance, protein levels of 50–200 mg/dl, and normal glucose levels with a negative bacterial culture and Gram stain. Group 4, with tubercular meningitis (TBM), was defined as those with a history of contact with a sputum-positive tuberculosis (TB) case, clinico-radiological

Table 1: Different types of meningitis according to age groups

Age	PM	PPM	VM	TBM	Control	Total
<2yrs	8	5	4	0	18	34
>2–5yrs	5	4	3	1	7	20
>5–10yrs	11	13	17	2	11	55
>10–15yrs	8	5	10	7	1	31
Total	32 (31.1%)	27 (26.2%)	34 (33%)	10 (9.7%)	37 (26.4%)	140

PM = pyogenic meningitis; PPM = partially treated meningitis; VM = viral meningitis; TBM = tubercular meningitis.

findings consistent with TB, and a positive reaction (>20 mm in duration) to 5 tuberculin units (TU) of purified protein derivative (PPD), and a CSF pleocytosis level of 10–500/mm^3 with predominant lymphocytes and a high CSF protein (100–3000 mg/dl), or in cases where a CSF culture and/or Ziehl-Neelsen staining have revealed acid-fast bacilli. Group 5, the control group, included those with a fever with convulsions but no meningitis. These convulsions were caused by epilepsy or febrile convulsions. Excluded from the study were those patients classified as neonates, those with fungal meningitis or concomitant illnesses such as human immunodeficiency virus (HIV). Patients with conditions contributing to an elevation of CSF CRP, such as infections other than meningitis and non-infectious conditions like rheumatic disorders, malignancies, and tissue injury, were also excluded,[8] as well as those on immunosuppressive therapy.

Statistical analysis was done using Epi-Info 3.5.2 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA). The test applied for statistics was an F-Test (i.e. analysis of variance [ANOVA] test). A *P* value of <0.05 was taken as statistically significant.

Table 2: Organisms isolated in blood and cerebrospinal fluid (CSF)

Organisms	Blood (n = 32)	CSF (n = 32)
Enterococcus	2	1
Pseudomonas	1	1
Escherichia coli	1	2
Staphylococcus aureus	0	2
Streptococcus pneumonia	0	2
Total	**4/32 (12.5%)**	**8/32 (25%)**

CSF = cerebrospinal fluid.

Results

The CSF from 140 children (32 PM, 27 PPM, 36 VM, 10 TBM, and 37 controls) was analysed. Table 1 shows the distribution of ages in both cases and controls. The greatest number of meningitis cases was noted in those aged 5–10 years, with bacterial meningitis (PM and PPM) predominating in all age groups [Table 1]. Organisms grown in the blood cultures were *Enterococcus*, which grew in two cultures; *Pseudomonas*, which grew in one culture, and *Escherichia coli*, which grew in one culture (4/32, 12.5%). Organisms isolated in CSF were *E. coli*, which was isolated in two samples; *Enterococcus*, which was isolated in one sample; *Staphylococcus aureus*, which was isolated in two samples; *Pseudomonas* was isolated in one sample; and *Streptococcus pneumonia*, which was isolated in two samples (8/32, 25%) [Table 2]. Blood CRP was positive in all groups [Table 4] with the highest values in the PM and PPM groups [Table 3], but they were not statistically significant (*P* <0.08). CSF CRP was significantly (*P* <0.001) higher in PM (45.75 ± 28.50) [Table 3]. Serum CRP sensitivity and specificity was 90.62% and 32.4% for PM; 88.88% and 30.97% for PPM; 64.7% and 24.52% for VM; 70% and 26.12% for TBM respectively [Table 5]. CSF CRP sensitivity and specificity was 96.87% and 74.73%, for PM; 66.66%, and 63.71% for PPM; 20.58% and 50.94%, for VM; 10% and 55.38% for TBM, respectively [Table 5].

Discussion

The aetiological diagnosis of meningitis remains a problem as the clinical and biochemical picture is often masked because of prior antibiotic use. This becomes even more difficult in a population like ours where patients first attend a private practitioner

Table 3: Laboratory parameters of different types of meningitis in blood and cerebrospinal fluid

Variables	PM Mean ± SD	PPM Mean ± SD	TBM Mean ± SD	VM Mean ± SD	Control Mean ± SD	*P* value
Blood						
CRP	**53.12 ± 28.88**	47.55 ± 34.34	39.60 ± 41.58	36.35 ± 38.00	31.13 ± 35.60	0.08
RBS	106 ± 29.84	98 ± 31.81	98 ± 29.85	88 ± 21.36	100 ± 30.72	0.14
CSF						
Total count	903.28 ± 1419	231.07 ± 303	158.40 ± 133	118.94 ± 246	.1081 ± .458	0.0001
Neutrophils	84.18 ± 12.26	60.37 ± 26.82	8.90 ± 8.22	10.88 ± 11.57	.000 ± .000	0.0001
Lymphocyte	15.81 ± 12.26	39.62 ± 26.82	90.60 ± 8.11	**86.23 ± 18.75**	**5.40 ± 22.92**	0.0001
Sugar	29.15 ± 15.11	47.44 ± 20.62	40.30 ± 13.69	55.00 ± 16.70	65.48 ± 16.75	0.0001
Protein	46.28 ± 32.89	43.85 ± 51.89	**256.90 ± 203**	30.05 ± 19.40	22.21 ± 28.80	0.0001
CRP	45.75 ± 28.50	23.11 ± 23.98	1.20 ± 3.79	4.47 ± 16.93	2.00 ± 8.84	0.0001

SD = standard deviation; PM = pyogenic meningitis; PPM = partially treated meningitis; TBM = tubercular meningitis; VM = viral meningitis; CRP = C-reactive protein; RBS = random blood sugar; CSF = cerebrospinal fluid.

The P value was determined by ANOVA test and <0.05 was considered as statistically significant value.

and receive a course of antibiotic. They then come to our hospital when they do not improve. In such a scenario, it becomes impossible to isolate the organisms from blood or CSF. Moreover, CSF cultures for pyogenic organisms are positive in only 30–60% of cases, according to various researchers.[9] In many places, facilities to isolate blood- or CSF-borne organisms is lacking and, if it is available, it can take a long time for culture reports to come. There is currently no single test to diagnose the aetiology of meningitis promptly and accurately; hence, a quick and reliable method is required for early bedside diagnosis. Our results suggest that serum CRP/CSF CRP in initial lumbar puncture is an ideal method in situations where it traditionally has been difficult to isolate organisms to aid with diagnosis. Passive diffusion across the highly inflamed meninges would be a reasonable explanation as to how CRP gains access to CSF.[10]

Meningitis was most frequently observed in the 5-to 10-year-old cohort. Neonates were not included in this study as there is no cut-off CRP titre for newborns, presumably due to the immaturity of the blood-CSF barrier (B1-CSF-B) during the first weeks of life.[6] Only 12.5% of the 32 cases of PM displayed organisms that had been isolated in blood cultures (*Enterococcus* [2], *Pseudomonas* [1], E. coli [1]). Likewise, 25% of the CSF cases displayed organisms in the blood cultures (E. coli [2], *Enterococcus* [1], *S. aureus* [2], *Pseudomonas* [1], *S. pneumoniae* [2]. In our study, the frequency of bacterial isolates in CSF was lower than that observed in other studies where it was 36% but the isolated organisms were similar to ours.[11]

Table 4: Occurrence of different types of meningitis in blood and cerebrospinal fluid

Study Groups	Blood CRP		CSF CRP	
	Positive	Negative	Positive	Negative
PM (n = 32)	29	3	31	1
PPM (n = 27)	24	3	18	9
VM (n = 34)	22	12	7	27
TBM (n = 10)	7	3	1	9
Control (n = 37)	20	17	2	35

CRP = C-reactive protein; CSF = cerebrospinal fluid; PM = pyogenic meningitis; PPM = partially treated meningitis; VM = viral meningitis; TBM = tubercular meningitis.

Table 5: Sensitivity and specificity for blood and cerebrospinal fluid C-reactive protein in different groups of meningitis

	Sensitivity (Sn)	Specificity (Sp)
CSF CRP		
PM	96.87%	74.73%
PPM	66.66%	63.71%
VM	20.58%	50.94%
TBM	10.00%	55.38%
BLOOD CRP		
PM	90.62%	32.40%
PPM	88.88%	23.68%
VM	64.47%	24.52%
TBM	70 %	26.12%

CSF = cerebrospinal fluid; CRP = C-reactive protein; PM = pyogenic meningitias; PPM = partially treated meningitis; VM = viral meningitis; TBM = tubercular meningitis.

In another study, the CSF cultures were positive for the presence of organisms in only 16% of cases.[12] The total count in CSF was 903.28 ± 1419.73 and the neutrophil count was the highest, at 84.18 ± 12.26. The glucose level in CSF was the lowest 29.15 ± 15.11 in PM, and was statistically significant (P <0.0001). Similarly, CSF lymphocyte levels (90.60 ± 8.11) and protein levels (256.90 ± 203.61) were highest in TBM cases, and were considered statistically significant (P <0.0001). Similar findings were noted in other studies.[12] These significant parameters may also be helpful in differentiating different types of meningitis but further studies with larger populations would be needed to assess this possibility as very little comparable data is available in this area.

Levels of CRP in serum and CSF increase as a result of invasive central nervous system infection.[4] Increased CRP production is an early and sensitive response to most forms of microbial infections and the value of its measurement in the diagnosis of various infective conditions was established in previous studies.[14,15] In this study, increased blood CRP levels were noted in all groups, but the difference was statistically insignificant (P >0.05 or = 0.08). In past studies, CRP levels were used to differentiate between bacterial and viral meningitis, since CRP levels are found to be lowest in viral meningitis.[4] Similarly, in our study, blood CRP level was lowest in viral meningitis (36.35 ± 38.00). Additionally, blood CRP was positive in 29/32 cases of PM, giving a sensitivity of 90.62%. Similar findings have been reported by other researchers.[16] The sensitivity for blood CRP was 88.88% (24/27) for PPM, 64.47% (22/43) for VM, and 70% (7/10) for TBM. The specificity for blood CRP was 32.40%, 30.97%, 24.52%, and 26.12% in PM, PPM, VM, and TBM, respectively. Different findings were noted in another study where serum CRP sensitivity for pyogenic meningitis was lower (76%) and specificity was higher (68%) than in our study.[17] Comparable data for other types of meningitis were not available. Blood CRP with a high sensitivity can be used as a screening test for different types of meningitis, but since the specificity was low in our study, its diagnostic accuracy has yet to be established. CSF CRP has been reported to be one of the most reliable and early indices to differentiate between bacterial and non-bacterial meningitis.[10,18] Corral *et al.* found positive CSF CRP in 24/32 patients with culture-proved bacterial meningitis, while only 2/32 children with non-bacterial meningitis had CSF which was positive for CRP. According to Corral *et al.*, this was a more sensitive test for differentiating bacterial from non-bacterial meningitis than any other laboratory test for CSF. Their study demonstrated that CSF CRP levels are also useful in diagnosing partially treated cases of meningitis. Our results also correlate with their findings.[2] The mean CRP in CSF in this study was significantly higher (P <0.0001) in patients with PM (45.75 ± 28.50) and PPM (23.11 ± 23.98) as compared to patients with TBM (1.20 ± 3.79), VM (4.47 ± 16.93), and controls (2.00 ± 8.84). CSF CRP was positive in 31/32 cases of PMs and 18/27 of those with PPM, giving it a sensitivity rate of 96.87% and 66.66%, respectively. Similar sensitivity for pyogenic meningitis was also reported in other studies.[16] In viral meningitis and TBM, CSF CRP sensitivity was low. The specificity for PM, PPM, VM and TBM was 74.73%, 63.71 %, 50.94%, and 55.38%, respectively. For pyogenic meningitis, a sensitivity of 84% and 94%, and a specificity of 100% have been reported by other researchers.[2,12] In another study, a sensitivity of 97%, which was similar to our study, and a specificity of 98% was observed.[19] Similarly, a sensitivity of 97% and specificity of 86% for bacterial meningitis was also reported by other researchers.[20] Comparable data for other types of meningitis were not available, so a definite conclusion for other types of meningitis cannot be made.

In this study, CSF as well as blood CRP sensitivity was high (CSF CRP > blood CRP) in PM, but in PPM, TBM, and VM, the sensitivity was higher in blood (blood CRP > CSF CRP). This indicates that CSF as well as blood CRP can be a good screening test for PM and blood CRP can be used as screening test for PPM, VM, and TBM. The specificity was higher in CSF CRP than blood CRP (PM = 74.73% *versus* 32.40%; PPM = 63.71% *versus* 30.97%; TBM = 55.38 % *versus* 26.12%; VM = 50.94% *versus* 24.52%). A high specificity of 94% in CSF CRP was noted by other studies for differentiating bacterial meningitis from both viral and normal forms of meningitis.[2,6] This indicates that CSF CRP is a better marker than serum CRP in differentiating bacterial meningitis from PPM, VM, or TBM. A similar view has been expressed by other researchers who found raised levels of CRP in CSF to be a better indicator of bacterial meningitis. It also served to distinguish

bacterial meningitis from viral and tubercular infections, and other central nervous system disorders.[21]

This study has a number of limitations. Primarily, our study included a small sample size. Thus, while determining CSF CRP levels is useful in screening for bacterial meningitis (PM, PPM), a further study with a larger population is required to assess its accuracy better in diagnosing different types of meningitis. Additionally, a larger control group would yield better statistics. A lack of virological laboratory support also may have affected the results of this study as PPM is a close differential diagnosis for VM. Finally, measuring CRP levels before and after antibiotics would give a better interpretation.

Conclusion

It can be concluded that assessing types of meningitis from CRP levels in CSF offers a high sensitivity and moderate specificity. It is a simple, rapid, and accurate method for making a laboratory diagnosis and is particularly appropriate for bacterial (both PM and PPM) meningitis. Blood CRP levels can also be used to screen for PM, PPM, VM, and TBM at bedside as such an assessment also offers high sensitivity. Based on our results, we recommend estimating CSF CRP and blood CRP levels in the routine evaluation of types of meningitis in children.

CONFLICT OF INTEREST

The authors report no conflict of interest in conducting this study and received no funding from any source.

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