



Original Research Article

The Significance of Serum C-Reactive Protein in Childhood Acute Meningitis

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Abstract

Serum concentrations of C-reactive protein is considered an important diagnostic test for sepsis because it increases several folds in response to bacterial infection. All over the world bacterial meningitis is a significant cause of childhood morbidity and mortality, so early diagnosis and treatment are the most important ways in prevention of the complications. The aim of this study was to estimate the usefulness of serum CRP level in differentiation between septic and aseptic meningitis. We measured the serum CRP level in patients who were diagnosed by clinical and laboratory findings as pyogenic and aseptic meningitis.

It was found that partially treated meningitis was most common in all age groups, and there is a significant correlation between high serum CRP titer and positive CSF culture p -value 0.004. Serum CRP was of high titer in 23 (82%) patients with pyogenic meningitis, while it was negative in 70% of patients with viral meningitis. Fever was the most common presenting symptom in all age groups 99 (90%) of patients. Patients with meningeal signs (neck stiffness) were 29 (87.8%) in those more than one year from total 33 patients and headache 19 (82.6%) from total 21 patients. There is a good sensitivity for serum-CRP, while there is a high specificity for CSF culture and a good specificity for CSF gram stain in pyogenic meningitis. CSF leukocyte polymorphs significantly increased in pyogenic meningitis, p -value 0.008. While lymphocytes significantly increased in viral meningitis, p -value 0.002. CSF protein: Increase >100 mg/dl in 86% of patients with pyogenic meningitis. CSF glucose was significantly decreased in pyogenic meningitis p -value 0.004.

We conclude from this study that serum CRP can help to distinguish between pyogenic and aseptic meningitis. Children who present with clinical features of meningitis in whom serum CRP values are determined at 12 hours after the onset of fever and are < 6 mg/L are less likely to have pyogenic meningitis. Serum CRP detection is not expensive, simple and dependable diagnostic indicator in meningitis.

Key words: C-reactive protein, pyogenic Meningitis, Aseptic meningitis.

أهمية مصل البروتين (سي) التفاعلي في التهاب السحايا الحاد عند الأطفال

الخلاصة

تركيزات مصل البروتين (سي) التفاعلي تزداد عدة مرات استجابةً للالتهابات البكتيرية، مما يجعله مهماً في الاختبار التشخيصي للتهاب السحايا القحبي. هو سبب مهم من أسباب أمراض الأطفال والوقيات في جميع أنحاء العالم. في العالم النامي، حيث عبء التهاب السحايا الحاد والعواقب طويلة الأمد بالأخص مرتفعة، فالتشخيص والعلاج المبكر هي الطرق الأكثر أهمية في الوقاية من المضاعفات. إن الهدف من الدراسة تقييم فعالية مستوى البروتين (سي) التفاعلي في مصل الدم في التفريق بين التهاب السحايا القحبي والمعقم. تم قياس مستوى بروتين (سي) التفاعلي في مصل الدم في المرضى الذين تم تشخيصهم بواسطة الموجودات السريعة والمختبرية أن لديهم التهاب السحايا الجرثومي والمعقم. لقد أظهرت نتائج هذه الدراسة أن التهاب السحايا المعالج جزئياً الأكثر شيوعاً في جميع الفئات العمرية، بالإضافة إلى وجود ارتباط كبير بين ارتفاع عيار بروتين (سي) التفاعلي ونتيجة إيجابية زرع السائل الدماغي الشوكي P -value.0.004. كان العيار العالي لبروتين (سي) التفاعلي في

الدم ايجابيا في (82%) 23 من المرضى الذين يعانون من التهاب السحايا القحي، في حين كان سلبيا في 70% من المرضى الذين يعانون من التهاب السحايا الفيروسي. كانت الحمى الميزة السريرية الأكثر شيوعا في جميع الفئات العمرية (90%) 99 من المرضى. الاختلاجات (80.3%) 41 من المرضى والقيء (86.2%) 44 من المرضى في أولئك الذين نقل اعمارهم عن سنة واحدة . وكان المرضى الذين يعانون من العلامة السحائية (تبيس الرقبة) (87.8%) 29 في أولئك الذين تزيد اعمارهم عن سنة واحدة من مجموع 33 مريضا والصداع (82.6%) 19 من إجمالي 21 مريضا. هناك حساسية جيدة، وقيمة تنبؤية سلبية لبروتين (سي) التفاعلي في الدم، في حين أن هناك خصوصية عالية وقيمة تنبؤية إيجابية لزرع السائل الدماغي الشوكي وخصوصية جيدة وقيمة تنبؤية سلبية لصبغة كرام (Gram) في السائل الدماغي الشوكي في السحايا الجرثومية. هناك زيادة كبيرة للكريات البيض عديدة الأشكال في السائل الدماغي الشوكي في التهاب السحايا القحي، P.value 0.008. بينما الخلايا الليمفاوية في التهاب السحايا الفيروسي، P.value 0.002. زيادة البروتين (>100mg) للسائل الدماغي الشوكي وجدت في 86% من المرضى الذين يعانون من التهاب السحايا القحي. معدل السكر في السائل الدماغي الشوكي قد انخفض بشكل ملحوظ في التهاب السحايا القحي P.value 0.004. نستنتج من هذه الدراسة ان البروتين سي التفاعلي في مصل الدم يمكن أن يساعد على التفريق بين التهاب السحايا القحي والمعقم، في المرضى الذين يعانون من التهاب السحايا الذين يتم تحديد قيمة بروتين (سي) التفاعلي لمصل الدم في على الأقل 12 ساعة بعد ظهور الحمى وهي (>6mg/L) هم أقل احتمالية أن يكون لديهم التهاب السحايا. تحديد قيمة بروتين (سي) التفاعلي في الدم طريقة قليلة الكلفة وبسيطة وموثوق بها كمؤشر للتشخيص في التهاب السحايا.

Introduction

When Creactiveprotein (CRP) has been used as a laboratory test in diagnosis of pyogenic meningitis, many researches have established that recognition of CRP in cerebrospinal fluid (CSF) or serum is of significance in differentiating the type of meningitis, and frequent measurements of CRP is of importance in checking the course of disease [1]. Meningitis has two main parts: Septic and aseptic meningitis. Septic meningitis was defined as the acute onset of meningitis and documented pyogenic infection in the CSF or serum ; Aseptic meningitis was defined as the acute onset of meningitis and the absence of any bacterial meningitis criteria. In pediatrics patients they developing severe disease of less than 24 hours, and in the absence of increased intracranial pressure, they should receive antibiotics rapidly after lumbar puncture (LP) is performed. If there are signs of increased intracranial pressure or focal neurologic deficit, antibiotics should be given without carrying out LP [2]. When inflammation or acute tissue destruction has occurred, CRP production increases within 4 to 6 hours; peaking at 36 to 50 hours, but with resolution of infection, it drops quickly because of relatively short

half-life of 4 to 7 hours [3]. Infants and young children with occult bacteremia have high risk of meningitis. The concentration of CRP in serum is many times higher than those in CSF, this discrepancy is explained by direct hepatic release of CRP into plasma which then undergo ultrafiltration to form CSF CRP. Meningeal irritation stimulates CRP production [4]. Since pyogenic sepsis is one of the most frequent diagnoses in neonatal medicine and classic diagnosis depend on culture of blood, cerebrospinal fluid (CSF), or urine and usually need waiting for a day or more, yet rapid progression of untreated infection may greatly increase risk of disease or even death [5]. For reducing morbidity and mortality of the patient we need fast and precise diagnosis together with early appropriate treatment. Biochemical tests, Cytology, Gram's stain, Culture and sensitivity of Cerebrospinal fluid usually being done to diagnose and differentiate septic from aseptic meningitis [7]. Serum CRP is considered one of the most important tests for differentiating septic from aseptic meningitis, its diagnostic precision in comparison with other laboratory tests need to be estimated [8]. CRP, an acute phase reactant,

has been used to make a diagnosis and follow up the course of disease[9].

Patients and Methods

Study Design

This is a prospective descriptive study, 110 patients (62males and 48 females) aged between 1mo. to 12 years admitted to Babylon Gynecology and Pediatrics Teaching Hospital, Hilla/ Iraq, From October 2013 to April 2014. Pyogenic meningitis was diagnosed by the distinctive clinical features, cerebrospinal fluid findings and culture.

Patients were considered as having pyogenic meningitis if CSF culture positive, CSF Gram's stain positive, and CSF contains >1000 leukocytes (polymorph predominant), and considered as having partially treated meningitis if they have received antibiotics for more than or equal to 24 hours, and as having viral meningitis if they not have received antibiotics and CSF contains leukocytes (lymphocyte predominant), we suggest viral meningitis because its common type and if there are points in history, physical examination and laboratory tests suggested tuberculosis, fungal, protozoal, poliomyelitis or other, we considered them but in this study samples those types not available in infectious word.

Serum CRP levels were estimated by a modified latex particle agglutination technique using a kit (AGAPPE DIAGNOSTIC SWITZERLAND GmbH). A semi-quantitative test has been used to

find out the titer of positive sample by the serial dilution methodology. CRP sensitivity = 6mg/L (when the test become positive before any dilution). High titer is equal to 192 mg/L (after five dilution). The lack of agglutination indicates that CRP level is lower than 6mg/L in the sample (negative result). Informed consent of parents has been taken.

Exclusion Criteria Include

1. Age <1 mo. because elevated CRP levels occur in association with many other conditions in addition to bacterial or fungal infections.
2. patients who don't have CSF findings suggestive of Meningitis.

Data Analysis

Data were analyzed by SPSS program, version 19 according to standard procedure. The descriptive analysis included frequency, chi-square test was used to estimate the correlation between variables. P value was considered significant when it is ≤ 0.05 .

Results

One hundred ten patients were studied during their admission to Babylon Gynecology and Pediatrics Teaching Hospital. From October 2013 to April 2014 with diagnosis of meningitis in its two forms, septic and aseptic category. Partially treated meningitis was most common in all age group and pyogenic meningitis was significant occur in less than one year age group p value 0.05. Table-1:

Table 1. Types of meningitis according to age

Type of meningitis	Age			Total	P value
	1 mo.-12mo.	13mo.-5yr.	5yr.-12yr		
Pyogenic	18	6	4	28	0.05
No.	64.2%	21.4%	14.2%	1000%	

Table 1. Types of meningitis according to age

Type of meningitis	Age			Total	P value
	1mo.-12mo.	13mo.-5yr.	5yr.-12yr		
Pyogenic No. %	18 64.2%	6 21.4%	4 14.2%	28 100%	0.05
Partially treated No. %	20 40.8%	15 30.6%	14 28.5%	49 100%	0.1
Viral or others No. %	13 39.3%	11 33.3%	9 27.2%	33 100%	0.2
P value	0.18	0.06	0.03		

In viral and partially treated bacterial meningitis males were predominant while in pyogenic meningitis females were predominant. Table 2.

Table 2:Types of meningitis according to the gender

Type of meningitis	gender		Total	P value
	male	female		
Pyogenic NO. %	12 42.9%	16 57.1%	28 100.0%	0.44
partially treated NO. %	33 67.3%	16 32.7%	49 100.0%	0.01
Viral or other NO. %	17 51.5%	16 48.5%	33 100.0%	0.86
Pvalue	0.002	0.06		

Fever was the most common clinical feature in all age group 99(90%) of patients. Convulsion 41(80.3%)of patients and vomiting 44(86.2%) patients in those

less than one year of age. Patients with neck stiffness were 29(87.8%) patients in those more than one year and headache 19(82.6%) patients. Table 3.

Table 3: Clinical features of meningitis according to type of meningitis and age groups.

Clinical features	Pyogenic meningitis			partially treated meningitis			viral		
	1mo.- 12mo.	13mo.- 5year	5-12 year	1mo.- 12mo.	13mo.- 5 year	5- 12year	1mo.- 12mo.	13mo.- 5 year	5-12 year
Fever NO. %	18 18%	6 6%	3 3%	20 20%	14 14%	11 11%	13 13%	7 7%	7 7%
Vomiting NO. %	14 20.8%	5 7.4%	3 4.4%	19 28.3%	6 8.9%	4 5.9%	11 16.4%	3 4.4%	2 2.9%
Convulsion NO. %	15 23.4%	2 3.1%	3 4.6%	13 20.3%	5 7.8%	6 9.3%	13 20.3%	4 6.2%	3 4.6%
Headache NO. %	1 4.3%	1 4.3%	2 8.6%	2 8.6%	4 17.3%	4 17.3%	1 4.3%	3 13.0%	5 21.7%
Meningeal signs NO. (Neck stiffness) %	1 3.1%	1 3.1%	2 6.2%	1 3.1%	7 21.8%	9 28.1%	1 3.1%	5 15.6%	5 15.6%

We compare serum C-reactive protein estimation with the result of CSF culture, One hundred ten patient (110) were included in this study, among them 28 (25.45%) patients had pyogenic meningitis, 18 (64.28%) of them have

yielded positive CSF culture, CSF Gram's stain was positive in 20 (71.42%) of patients and the remaining eight patients had CSF polymorph > 1000 cell/mm³, in this study there is significant correlation between high serum CRP titer and positive CSF culture p.value 0.004. Table 4

Table 4: serum CRP titer with CSF culture result

Serum CRP	CSF culture			P value
	negative	positive	Total	
<6mg/L No. %	65 100%	0 0%	65 100.0%	0
12mg/L No. %	12 100%	0 0%	12 100.0%	0.005
24mg/L No. %	10 83.3%	2 16.7%	12 100%	0.02
48mg/L NO. %	4 57.1%	3 42.9%	7 100%	0.7
96mg/L No. %	1 16.7%	5 83.3%	6 100%	0.1

192mg/L	No. %	0 0%	8 100%	8 100%	0.004
Total	NO. %	92 83.6%	18 16.3%	110 100%	

Serum CRP was of high titer in 23 (82%) patients with pyogenic meningitis, while is negative in 70% of patients with viral meningitis.

Table 5: CRP titer according to type of meningitis.

Serum CRP	Type of meningitis			Total
	Pyogenic	partially treated	Viral or other	
<6mg/L	5 7.6%	37 56.9%	23 35.3%	65 100.0%
12mg/L	0 0%	5 41.6%	7 58.3%	12 100.0%
24mg/L	5 41.6%	4 33.3%	3 25.0%	12 100.0%
48mg/L	4 57.1%	3 42.8%	0 0%	7 100.0%
96mg/L	6 100.0%	0 .0%	0 .0%	6 100.0%
192mg/L	8 100.0%	0 0%	0 0%	8 100.0%
Total	28 25.5%	49 44.5%	33 30.0%	110 100.0%

There is a good sensitivity, negative predictive value of serum-CRP, while there is a high specificity and positive predictive value for CSF culture and

a good specificity and negative predictive value for CSF Gram stain in pyogenic meningitis: Table 6.

Table 6:Sensitivity, Specificity, positive and negative predictive value of serum –CRP, CSF culture, and CSF- Gram stain in pyogenic meningitis

Lab finding	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
Serum CRP	82.14%	73.17%	51.11%	92.30%
CSF culture	82.14%	100%	100%	86%
CSF gram stain	71.42%	95.12%	83.33%	90.6%

CSF leukocyte polymorphs significantly increased in pyogenic meningitis, pvalue 0.008. while lymphocytes significantly increased in viral meningitis, p value 0.002. CSF protein Increase >100mg/dl in

86% of patients with pyogenic meningitis. CSF glucose was significantly decreased in pyogenic meningitis pvalue 0.004. table 7.

Table 7:CSF laboratory findings according to type of meningitis.

CSF finding	pyogenic meningitis		Partially treated meningitis		viral		P value
	No.	%	No.	%	No.	%	
CSF polymorph Dominant	23	82	18	37	3	9	0.008
CSF lymphocyte Dominant	5	18	31	63	30	91	0.002
CSF protein normal <100mg/dl Increase >100mg/dl	4	14	19	39	17	52	1 0.02
	24	86	30	61	16	48	
CSF glucose > 45mg/dl < 45mg/dl	15	53.5	30	61	31	94	0.004
	13	46.5	19	39	2	6	

Discussion

In this study, partially treated bacterial meningitis was the most common type of meningitis (44.5%) which goes with AbdStudy[2](36%). While in Piyushsadatetal study [4]. It was the least one (11%). This might be due to antibiotic use before diagnosis.

In viral and partially treated bacterial meningitis males were predominant while in pyogenic meningitis females were predominant. In Sharad Bansal et al study [6] and Belal Uddin et al study [7], males were predominant in all types of meningitis. Fever was the most common clinical feature in pyogenic meningitis 27(96.4%)

patients followed by vomiting 22(78.5%) patients and convulsion 20(71.4) in patients. Neck stiffness 4(14.3) and headache 4(14.3), while in PiyushSadatetal study[4] fever was 83% and convulsion 83% headache was present in 16% and vomiting 33% of patients.

Fever was the most common clinical feature in all age groups 99(90%) of patients. convulsion 41(80.3%) of patients and vomiting 44(86.2%) patients in those less than one year of age. Patients with neck stiffness were 29(87.8%) in those more than one year from total 33 patients and headache 19(82.6%) from total 21 patients.

We confirmed that the sensitivity of serum CRP is 82.14% and its specificity is 73.17% which is higher than Col PL Prasad etalstudy[9].(sensitivity 76% and its specificity(68%). Raised level of combined CRP in CSF and serum were found to be sensitive in 96% and specific in 100% of cases. Positive predictive value of raised CRP in CSF alone was 94% and in combination with raised serum C-RP was 100%. Negative predictive value of raised CRP in CSF alone was 82% and in combination with serum CRP was 93%[7], however, its diagnostic precision in comparison with other laboratory tests is needed to be estimated[9].

The titer of serum CRP in our study was high in 82% of pyogenic meningitis, while is low in patients with partially treated bacterial meningitis and viral meningitis(24% and 30%) respectively. In AbdStudy[2], serum CRP was positive in 53% of patients with bacterial meningitis, 18% of patients with viral meningitis, and 25% of patients with partially treated bacterial meningitis. Tankhiwale [10]. showed that serum CRP was positive in 88% of pyogenic meningitis. Serum CRP test was positive in 100% of cases of meningitic groups and 53% of non meningitic group[11].

Cerebrospinal fluid polymorph was present in 82% of patients with pyogenic meningitis this result is in agreement with Piyushsadatetal[7], and RafezaKhanamet.

al[12] studies (83% and 85%) respectively.

Cerebrospinal fluid sugar decreased in 46.5% of pyogenic M., while in Piyushsadatetal [7] is 16.6% and Abdstudy[2] is 95%.

Cerebrospinal fluid protein increased in 86% of our pyogenic M. patients. CSF protein was high (>100 mg/dl) in 90% of bacterial meningitis in Abd study[2] these results pointed out that CSF pleocytosis and protein are more useful predictors of pyogenic meningitis than CSF sugar.

Conclusion

Although culture of CSF is the gold standard for diagnosis of pyogenic meningitis for direct evidence of the organism, it has some limitations particularly in peripheral set up and it takes 72 hr. for the result to be at hand. Routine detection of serum C-reactive protein could be a reliable, rapid and easy to be done test for the diagnosis of pyogenic meningitis and differentiating it from aseptic meningitis. It is not an alternative of examination of CSF biochemistry, cytology, and culture.

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