C Reactive Protein for Differentiating Bacterial from Aseptic Meningitis in Thai Patients

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Objectives: *To evaluate the efficacy of serum CRP level differentiating between bacterial and aseptic meningitis in Thai patients.*
Material and Method: *The authors measured the serum CRP level in patients who were diagnosed clinically as bacterial and aseptic meningitis.*
Results: *The authors evaluated 32 subjects; 12 with bacterial meningitis (all males) and 20 with aseptic meningitis (13 males; 7 females). The mean serum CRP level in the bacterial meningitis and aseptic meningitis group was 209.25 $\pm$ 105.34 (range, 65 to 420) and 67.05 $\pm$ 40.81 (range, 10 to 169) mg/L, respectively ($p < 0.001$).*
Conclusions: *serum CRP can help differentiate between bacterial and aseptic meningitis.*

Keyword: *Serum CRP, Bacterial meningitis, Aseptic meningitis*

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C reactive protein (CRP) is a reactive protein of the acute inflammatory process or infectious process[1-4]. Normally, serum CRP should not be detected or should be found less than 10 mg/L[5,6]. It will be markedly and rapidly raised if the inflammatory or infectious process occurred. In the diagnosis and management of bacterial meningitis, especially in children, the serum CRP level has been reported[7-9]. Furthermore, the high sensitivity CRP can also determine the risk of coronary artery disease[10].

Acute meningitis is mainly caused by bacterial, viral, rickettsia or spirochete infection. Precise diagnosis is possible if the cerebrospinal fluid Gram stain or culture identifies the pathogen. There are some ambiguous cases between bacterial and viral meningitis such as neutrophilic predominate in viral meningitis[11-13] or an unidentified pathogen in bacterial meningitis. The diffentiation between viral and bacterial meningitis is very important in treatment. The authors did a study to evaluate the efficacy of serum CRP in differentiating between bacterial and aseptic meningitis.

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Material and Method

The authors recruited patients clinically diagnosed as having acute meningitis at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. At the time of diagnosis, all patients were assessed for their serum CRP level, complete blood count, hemoculture, and cerebrospinal fluid (CSF) for white blood cell count, differential count, protein, glucose, Gram stain, acid fast stain, culture, and latex agglutination.

The studied cases were differentiated into two groups; bacterial meningitis or aseptic meningitis. Neutrophilic predominated CSF or positive Gram stain suggested the diagnosis of bacterial meningitis. CSF culture, CSF for latex agglutination test, or hemoculture was used to confirm the diagnosis. The follow up CRP level was done up to the clinical judgement by primary care physicians. On the other hand, aseptic meningitis was diagnosed in cases of lymphophilic CSF with the normal CSF glucose level. The negative result on CSF for latex agglutination test, CSF Gram stain, CSF culture, and hemoculture confirmed the diagnosis of aseptic meningitis.

Latex agglutination test, the test of bacterial antigen kit, was used to detect bacterial antigen of Streptococcus group B, Hemophilus influenzae type B, Streptococcus pneumoniae, Neisseria meningitides group A and C, and Escherichia coli.

The serum CRP level was measured using the turbidimetric method by a Behring nephelometer and the specific Behring N Latex CRP reagent (Roche Diagnostics) at the Clinical Immunology Unit, Srinagarind Hospital.

The main outcome was to test the difference of serum CRP level between bacterial and aseptic meningitis by using the student t test. The secondary outcome was to evaluate the serum CRP level after treatment.

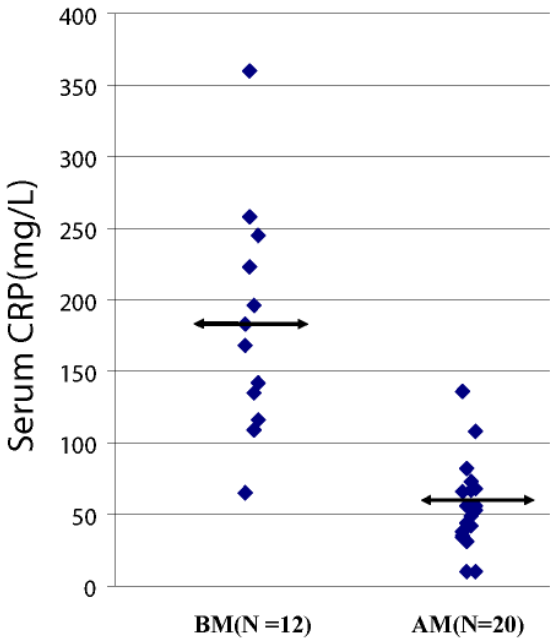
Results

Thirty-two cases were enrolled: 12 with bacterial meningitis (all males) and 20 with aseptic meningitis (13 males; 7 females). The median age at diagnosis among all patients was 22 (range 1 to 79, mean $\pm$ SD = 25.47 $\pm$ 19.82). The mean age of the bacterial vs aseptic meningitis groups was 28.83 $\pm$ 24.11 vs 23.45 $\pm$ 17.11years, respectively.

Twelve cases of bacterial meningitis were diagnosed clinically with neutrophilic CSF with the positive CSF Gram stain, or confirmation by hemoculture, CSF culture, or latex agglutination. The hemoculture was positive in 5 cases (Streptococcus pneumoniae 2; Salmonella gr. B 1; Hemophilus ducreyi 1; Enterococci 1); CSF culture was positive in 4 (S. pneumoniae 3, Salmonella gr. B 1); CSF Gram stain was positive in 9. Latex agglutination was positive in 2 cases; both were S. pneumoniae (Table 1). By contrast, aseptic meningitis was diagnosed clinically by lymphocytic pleocytosis in the CSF and negative in all the same tests (hemoculture, CSF culture, CSF Gram stain and CSF latex agglutination) as shown in Table 2.

The serum CRP level was measured on the day of admission. The mean serum CRP level in the bacterial meningitis and aseptic meningitis group was 209.25 $\pm$ 105.34 (range, 65 to 420) and 67.05 $\pm$ 40.81 (range, 10 to 169) mg/L, respectively ($p < 0.001$) (Fig. 1).

The authors followed-up the serum CRP levels in 2 cases of bacterial meningitis (S. pneumoniae; case no.12 and Enterococci; case no.8). The serum CRP levels for Streptococcal meningitis vs Enterococcal meningitis on the 1st, 3rd and 15th day of admission were 420, 140 and 23 mg/L vs 258, 120, 30 mg/L, respectively (Fig. 2). On the 3rd day of admission, both patients were afebrile and clinically responsive to a 2-week course of antibiotics.



$P < 0.001$

Note: BM; bacterial meningitis, AM; aseptic meningitis, ⟷; mean value of serum CRP

Fig. 1 Comparing serum CRP level of bacterial vs aseptic meningitis

Dicussion

Serum CRP is a reactive protein, activated by the acute inflammatory process or acute infection particularly bacterial. Macrophages located at the inflammatory site, such as the meninges, will release cytokines (Interleukin-1, Interleukin-6, and tumor necrotic factor). IL-6 is the major factor that stimulates hepatocytes to produce CRP. The CSF CRP level has been reported lower than the serum CRP level[14]. The serum CRP level can help to differentiate between bacterial and viral meningitis, especially in children[15-17]. The presented data showed that there were significant differences between these two types of meningitis in Thai subjects. It can also be implied that the serum CRP level may make diagnosis clearer in cases with clinical suspicious of bacterial meningitis and corroborative lab work, for example; negative for CSF Gram stain or lymphocytic CSF, or aseptic meningitis with neutrophilic CSF. Furthermore, it may differentiate bacterial meningitis and leptospirosis or scrub typhus in Thai patients.

The authors also followed-up serum CRP levels in 2 cases of bacterial meningitis (S. pneumoniae and Enterococci). On the 3rd day of admission, both

Table 1. Clinical characteristics of bacterial meningitis group

No.	Sex	Age (Y)	CSF profile								Hemoculture	serum CRP (mg/dL)
			WBC (cells/mm^3)	% PMN	% MO	% EO	Protein (mg/dL)	Sugar (mg/dL)	G/S	LA	C/S	
1	M	30	1825	90	10	-	116	47/132	GPDC	-	S. pneumoniae	S. pneumoniae	183
2	M	1	200	90	10	-	-	10/129	GNB	-	Salmonella gr.B	Salmonella gr.B	223
3	M	3	2300	83	11	6	694	50/167	GPDC	S. pneumoniae	S. pneumoniae	S. pneumoniae	196
4	M	5	825	80	20	-	895	10/79	GPDC	-	-	-	116
5	M	8	1020	76	18	6	102	34/106	-	-	-	H. ducreyi	168
6	M	50	5260	90	10	-	44	49/169	GNB with capsule	-	-	-	360
7	M	79	4720	97	3	0	327	51/70	GPDC	-	-	-	135
8	M	19	1400	80	20	0	540	30/130	-	S. pneumoniae	-	-	278
9	M	36	1100	50	49	1	96	50/103	GPDC	-	-	-	65
10	M	47	2580	55	45	0	168	74/210	GNB	-	-	Enterococci	258
11	M	19	2400	90	10	0	129	36/108	GPDC	-	-	-	109
12	M	49	422	80	12	0	744	146/10	-	-	S. pneumoniae	-	420
Mean		28.8											209.25
SD		24.1											105.34

Note: Y; years, CSF; cerebrospinal fluid, CRP; C-reactive protein, WBC; white blood cell, PMN; neutrophil, MO; mononuclear cell, Eo; eosinophil, Sugar; CSF sugar/plasma glucose, G/S; Gram stain, LA; latex agglutination test, C/S; culture and sensitivity, M; male, GPDC; Gram positive diplococci, GNB; Gram negative bacilli, SD; standard deviation

Table 2. Clinical characteristics of aseptic meningitis group

No.	Sex	Age (Years)	CSF profile					serum CRP (mg/dL)
			WBC (cell/mm^3)	%PMN	%MO	Protein (mg/dL)	Sugar (mg/dL)	
1	F	2	159	19	81	102	24/72	38
2	M	20	145	22	78	94	57/130	10
3	M	18	78	10	90	21	83/173	73
4	M	11	388	10	90	95	50/135	56
5	M	34	160	9	91	156	48/114	136
6	F	1	60	30	70	14	62/83	31
7	M	53	130	15	85	120	39/110	42
8	F	13	102	21	79	26	60/100	68
9	F	18	100	30	70	134	60/126	124
10	F	24	25	20	80	110	47/146	82
11	M	49	50	5	95	25	116/120	67
12	M	4	5	14	86	132	78/123	108
13	M	36	140	13	87	171	51/120	66
14	F	13	145	1	99	60	81/146	56
15	M	53	480	14	86	112	83/266	169
16	M	8	160	8	92	56	48/104	10
17	M	36	80	18	82	69	71/110	35
18	M	29	178	17	83	74	83/167	44
19	M	5	160	4	96	88	68/95	73
20	F	42	80	3	97	144	78/111	53
Mean		23.45						67.05
SD		17.11						40.81

Note: CSF; cerebrospinal fluid, CRP; C-reactive protein, WBC; white blood cell, PMN; neutrophil, MO; mononuclear cell, EO; eosinophil, Sugar; CSF sugar/plasma glucose, M; male, F; female, S.D.; standard deviation

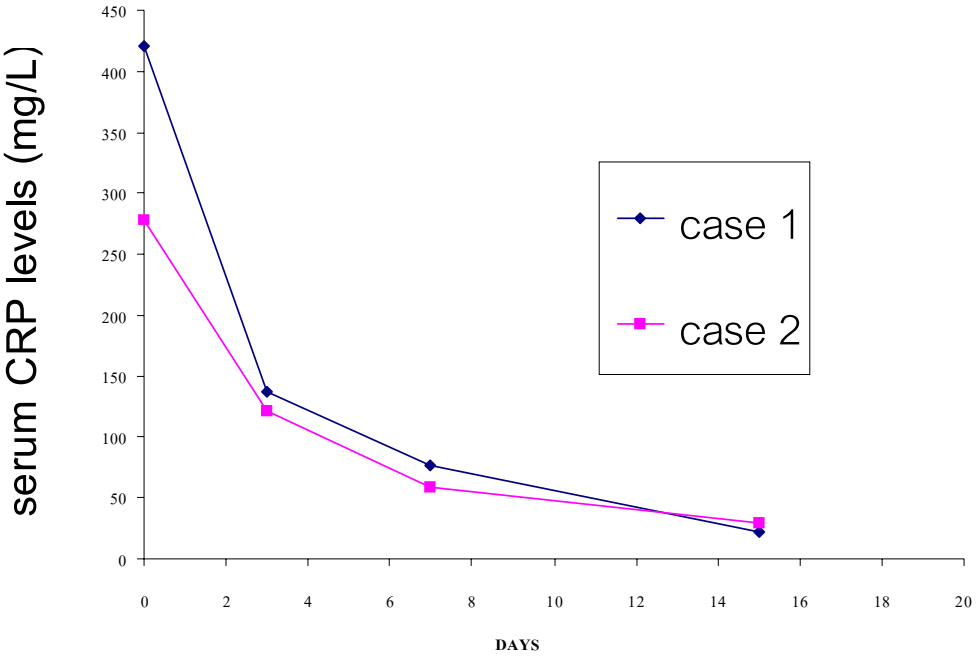


Fig. 2 Serum CRP level after treatment (days) in two cases of bacterial meningitis

patients had improved clinicals. The authors observed the decrease in serum CRP levels of more than 50% by day 3 and near normal by day 15. Serum CRP levels can be used in follow-up; to confirm the clinical status of the patient, and to search for complications of meningitis. Peltola et al reported that serum CRP levels in cases of bacterial meningitis will decrease to normal levels within 7 to10 days if the patient responds to treatment and is still a complicated case of meningitis with subdural effusion[15]. Unfortunately, the authors could not have complete data at the follow up of all patients because some patients denied laboratory test after clinical improvement and missing data at the time of follow up.

The latex agglutination test was used to detect bacterial antigen in the CSF. The sensitivity varies between 3 and 91%[8,17]. The present study detected two positive cases among 12 of bacterial meningitis. The kit, reagent, method of test, or infective organism may influence the results of the test. Some studies suggest using this test only in cases of suspected bacterial meningitis[18,19]. In summary, the latex agglutination has quite a low sensitivity.

Conclusion

The serum CRP level is a useful tool for differentiating between bacterial meningitis and aseptic meningitis in cases of uncertain diagnosis and for looking for complications of bacterial meningitis.

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References

1. Ballou SP, Kushner I. C-reactive protein and the acute phase response. Adv Intern Med 1992; 37: 313-6.
2. Gabay C, Kushner I. Acute phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 11: 448-54.
3. Kushner I. C-reactive protein and the acute phase response. Hosp Pract 1990; 30: 13-28.
4. Hansson LO, Lindquist L. C reactive protein: its role in the diagnosis and follow-up of infectious diseases. Curr Opinion in Infectious Disease 1997; 10: 196-201.
5. Claus DR, Osmand AP, Gewurz H. Radioimmunoassay of human C reactive protein and levels in normal sera. J Lab Clin Med 1976; 87: 12-8.
6. Palosuo T, Thusman T, Koistinen J. C reactive protein in population samples. Acta Med Scan 1986; 220: 175-9.
7. Loretta Wubbel DO, George H, McCragken JR. Management of bacterial meningitis. Pediatric in Review 1998; 19: 78-84.
8. Gray LD, Pedorko DP. Laboratory diagnosis of bacterial meningitis. Clin Microbiol Rev 1992; 5: 130-45.
9. Putto A, Ruuskanen O, Meurman O. C-reactive protein in the evaluation of febrile illness. Arch Dis Child 1986; 61: 24-9.
10. Libby P, Ridker PM. Inflammation and atherosclerosis: role of C-reactive protein in risk assessment. Am J Med 2004; 116(Suppl 6A): 9S-16S.
11. Somekh E, Cesar K, Handsher R. An outbreak of echovirus 13 meningitis in central Israel. Epidemiol Infect 2003; 130: 257-62.
12. Bottner A, Daneschnejad S, Handrick W. A season of aseptic meningitis in Germany: epidemiologic, clinical and diagnostic aspects. Pediatr Infect Dis J 2002; 21: 1126-32.
13. Negrini B, Kelleher KJ, Wald ER. Cerebrospinal fluid findings in aseptic versus bacterial meningitis. Pediatrics 2000; 105: 316-9.
14. Gray BM, Simmons DR, Mason H. Quantitative levels of C-reactive protein in cerebrospinal fluid in patients with bacterial meningitis and other conditions. J Pediatr 1986; 108: 665-70.
15. Peltola H, Rasanen JA. Quantitative C-reactive protein in relation to erythrocyte sedimentation rate, fever, and duration of antimicrobial therapy in bacteremic diseases of childhood. J Infect 1982; 5: 257-67.
16. Paradowski M, Lobos M, Kuydowicz J. Acute phase proteins in serum and cerebrospinal fluid in the course of bacterial meningitis. Clin Biochem 1995; 20: 459-66.
17. Kiska DL, Jones MC, Magnum ME. Quality assurance study of bacterial antigen testing of cerebrospinal fluid. J Clin Microbiol 1995; 35: 1141-4.
18. Phillips SE, Millan JC. Reassessment of microbiology protocol for cerebrospinal fluid specimens. Lab Med 1991; 22: 619-22.
19. Rodewald LE, Woodin KA, Szilagil PG. Relevance of common tests of cerebrospinal fluid in screening for bacterial meningitis. J Pediatr 1991; 119: 363-9.

การแยกภาวะเยื่อหุ้มสมองอักเสบจากเชื้อแบคทีเรียจากเยื่อหุ้มสมองอักเสบชนิดอะเสพติกในผู้ป่วยชาวไทยโดยซีอาร์พี

สุชาติ ศิริชัยชิงกุล, สมศักดิ์ เทียมเก่า, กิตติศักดิ์ สวรรยาวิสุทธิ์, วีรจิตต์ โชติมงคล

วัตถุประสงค์: *เพื่อประเมินผลการใช้การตรวจซีรัมซีอาร์พีเพื่อแยกภาวะเยื่อหุ้มสมองอักเสบจากเชื้อแบคทีเรียจากเยื่อหุ้มสมองอักเสบชนิดอะเสพติกในผู้ป่วยชาวไทย*

วัสดุและวิธีการ: *วัดระดับซีรัมซีอาร์พีในผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นเยื่อหุ้มสมองอักเสบจากเชื้อแบคทีเรียและเยื่อหุ้มสมองอักเสบชนิดอะเสพติกตั้งแต่แรกวินิจฉัยโดยอาศัยลักษณะทางคลินิก*

ผลการศึกษา: *มีผู้ป่วยที่เข้าร่วมการศึกษาจำนวน 32 ราย (ผู้ป่วยชาย 12 รายที่ได้รับการวินิจฉัยว่าเป็นเยื่อหุ้มสมองอักเสบจากเชื้อแบคทีเรีย, ผู้ป่วยชาย 13 รายและหญิง 7 รายที่ได้รับการวินิจฉัยว่าเป็นเยื่อหุ้มสมองอักเสบชนิดอะเสพติก) ค่าเฉลี่ยของซีรัมซีอาร์พีในผู้ป่วยกลุ่มที่ได้รับการวินิจฉัยว่าเป็นเยื่อหุ้มสมองอักเสบจากเชื้อแบคทีเรียและเยื่อหุ้มสมองอักเสบชนิดอะเสพติกเท่ากับ 209.25 + 105.34 (ระหว่าง 65 ถึง 420) และ 67.05 + 40.81 (ระหว่าง 10 ถึง 169) มก/ลิตร, ตามลำดับ ($p < 0.001$)*

สรุป: *ระดับซีรัมซีอาร์พีสามารถใช้แยกโรคเยื่อหุ้มสมองอักเสบจากเชื้อแบคทีเรียและเยื่อหุ้มสมองอักเสบชนิดอะเสพติกในผู้ป่วยชาวไทยได้*