ORIGINAL ARTICLE

Cerebrospinal Fluid C-reactive Protein in the Diagnosis of Meningitis in Children

by

*SOETIMAN SOETIONO,, SUNARTINI, SOEROYO MACHFUDZ, and SETYAWATI P.S.**

*(From the Child Health Department, and the *Clinical Pathology Laboratory, Gajah Mada University, School of Medicine, Yogyakarta/Dr. Sardjito General Hospital, Yogyakarta)*

Abstract

The mortality rate of bacterial meningitis in infants and children is still high (40–50%). Such a mortality rate can be reduced by establishing a prompt and accurate diagnosis. Until now the diagnosis of meningitis is still an important clinical problem.

The examination of cerebrospinal fluid C-reactive protein had been done in 44 clinical meningitis patients in the Paediatrics Department, Dr. Sardjito General Hospital qualitatively by means of latex agglutination slide test. Cerebrospinal fluid C-reactive protein was positive in 90% (18/20) of bacterial meningitis patients compared to 8.3% (2/24) of non bacterial meningitis patients. The sensivity and specificity of cerebrospinal fluid C-reactive protein were 90% and 91.7% respectively and these value were more sensitive and specific than those of white cell count, absolute polymorphonuclear, glucose and protein levels and the cerebrospinal fluid smear (50–80% and 80–91% respectively) which had been performed in the diagnosis of meningitis.

It can be concluded that the examination of cerebrospinal fluid C-reactive protein can be used as a diagnostic tool of bacterial meningitis.

Presented at KONIKA VII Jakarta, Sept. 1987.

Introduction

Bacterial meningitis is a serious infection especially among infants and children with a high mortality rate (40–60%) (Bell and Mc Cormick, 1981; Kaiser and Mc Gee, 1984). A prompt and accurate diagnosis of bacterial meningitis has been a problem since the cerebrospinal fluid examination, which is usually conducted, is heavily influenced by early antibiotics treatment, and thus, produces lower sensitivity and specificity (Bell and Mc Cormick, 1981; Corral et al., 1981). Since the expected culture of microorganism takes time to grow (5–7 days), antibiotics should be given; prompt results and high sensitivity and specificity should be invented.

C-reactive protein is an acute phase reactant invented by Tillet and Francis in 1930. It is called so because of its ability to precipitate the C somatic polysaccharide pneumococcus. Loid and Avery in 1941 succeeded in separating and purifying it from the serum. (Sonnenwirth, 1970; Pepys, 1981). C-reactive protein is a globulin produced by liver cells on the interlequin 1 stimulation (Pepys, 1981; Florman, 1985).

Its level in the serum and other closed organ fluids immediately rises few hours since the onset of systemic bacterial infection in the closed organs (Shaffer and Golden, 1969; Pepys, 1981; Florman, 1985).

Semi-quantitative and quantitative examinations of C-reactive protein serum have commonly been conducted to distinguish bacterial and non bacterial infections (Mc Carthy et al., 1978; Peltola, 1982; Clarke et al., 1983; Peltola et al., 1984; Komoroski et al., 1977). Quantitative examination is able to diagnose and to detect bacterial infection in children and neonates (Peltola, 1982; Peltola, 1983; Mc Pherson,1984; Philip and Baker, 1983; Philip, 1985). Quantitative examination of C-reactive protein of cerebrospinal fluid has been proved and can be used to differentiate bacterial meningitis from non bacterial one (Gray et al., 1985). Yet, quantitative C-reactive protein examination needs a lot of time and difficult procedures, and that, qualitative C-reactive protein examination by means of latex agglutination slide test, which is simpler and quicker, is necessary to be put to the test (Sonnenwirth, 1970).

It has been proved that qualitative C-reactive protein serum examination cannot be used to distinguish bacterial infections from non bacterial one. It is because some viral infection, even of low level, is able to stimulate the emerging of C-reactive protein (Ruuskanen et al., 1985; Florman, 1985). Qualitative C-reactive protein examination slide test can be done in bed side during 5–10 minutes (Mac Farlane and Narla, 1985).

Qualitative C-reactive protein examination of cerebrospinal fluid according to Corral et al. (1981) has 100% sensitivity and 98.6% specificity, while according to Mac Farlane and Narla (1985) it has 97% sensitivity and 98.6% specificity. But, other researcher has found lower sensitivity of only 60% from the same examination method (Waterspiel, 1983). Therefore, re-examination of the use of qualitative C-reactive protein of cerebrospinal fluid as means to diagnose bacterial meningitis is essential.

Materials and Methods

The investigation was performed in the Paediatrics Department of Dr. Sardjito General Hospital since the first of May 1986 to 30th June 1987. The subjects of this study were patients with the following symptoms: body temperature of 37° C., meningeal sign or convex fontanelle, decreasing consciousness, and abnormal neurological convulsion. Patients with rheumatic fever, rheumatoid heart disease, and severe and active leprosy were excluded from the study.

At admission samples of blood and cerebrospinal fluid of all defined patients were taken aseptically through lumbar puncture. Examinations of the amount of leucocyte, temporary variety of glucose level, latex agglutination slide test of qualitative C-reactive protein, and microorganism culture were carried out from the blood samples. The examinations in purity, pressure, colour, None, Pandy, number of cells, glucose and protein levels, and microorganism by means of smear preparation were conducted on the cerebrospinal fluid samples. Cellular and biochemical examinations, which had to be done within 15–50 minutes and 1–12 hours respectively after sample collection were done in the Clinical Laboratory of Dr. Sardjito General Hospital/the Clinical Pathology Laboratory of Gadjah Mada University School of Medicine. Microorganism examination was conducted in the Microbiology Laboratory of Gadjah Mada University, School of Medicine.

The culture of microorganism of both blood and cerebrospinal fluids was taken to the Microbiology Laboratory by transporting medium for anaerob and aerob bacteria. Each material of 1 cc was put in two different tubes of 9 cc thioglycolat medium for the anaerob and of 9 cc Brain Heart Infusion for the aerob. They were incubated for 2 – 7 days in the temperature of 37° C. When the microorganism grew they were planted again in the GAM blood agar (anaerob) and in the Mc Conkey blood agar (aerob) and were reincubated for 24 – 48 hours in 37° C. Then anaerob bacteria were identified by biochemical test on petri dish by incubating it in 37° C for 2 – 5 days, and the results could be interpreted. Aerob bacteria were identified in the biochemical lines of LIA, KIA, SSS, and MIO with 37° C incubation for 24 hours, and the results could be interpreted by the use of table.

The examinations of microorganism culture and smear preparation were conducted to indentify the suspected patients with tuberculous meningitis. But, due to the limitation of laboratory capability, viral identification and its laceration was not carried out.

Cerebrospinal fluid qualitative C-reactive protein examination was conducted by using latex agglutination slide test. The test is positive when the agglutination is distinctively visible and is negative when there is vague agglutination or light granulation devoid of agglutination (in accordance with the control). Statistical trials in this study used diagnostic test.

Results and Discussion

There were 44 clinical meningitis patients of which, by examination of microorganism culture, 20 patients were of bacterial meningitis, and by examinations of both microorganic culture and smear preparation, the other 24 patients were unknown

causes. The causal bacteria were as follows: Streptococcus group B (6), *Staphylococcus aureus* (4) *Streptococcus penumoniae* (4), Pseudomonas (3), Klebsiela (2), and *Myco bacterium tuberculosis* (1). The outcome of smear preparation of microorganic detection was 55% (11/20) (table 1). This lower outcome of smear preparation was possibly caused by the fact that 80% (16/20) of the bacterial meningitis patients had already received antibiotics before their admission to the hospital. This is similar to the results of previous investigations (Bell and Mc Cormick, 1981; Corral, et al., 1981).

Table 1 : *Types of causal bacteria of bacterial meningitis*

Causal bacteria	n	Culture %	Smear Preparation Positive	%	Negative	%
Streptococcus group B	6	30	3	15	5	15
Staphylococcus aureus	4	20	3	15	1	5
Streptococcus penumoniae	4	20	3	15	1	5
Pseudomonas	3	15	0	0	3	15
Klebsiela	2	10	2	10	0	0
Mycobacterium tuberculosis	1	5	0	0	1	5
Total	20	100	11	55	9	45

Positive C-reactive protein serum was identified in 18 out of 20 bacterial meningitis patients, and 8 out of 24 non bacterial meningitis patients, and that C-reactive protein serum had sensitivity of 90% (18/20) but low specificity of 67% (16/24). Positive predictive value of C-reactive protein serum was as low as 69% (18/26), but its negative predictive value was as high as 89% (16/18) (table 2).

Table 2 : *The outcomes of C-reactive protein serum examination of meningitis patients*

C-RP	Bacterial meningitis	Non bacterial meningitis	Total
Positive	18	8	26
Negative	2	16	18
Total	20	24	44

Sensitivity = 90% (18/20) Positive predictive value = 69% (18/26)
Specificity = 67% (16/24) Negative predictive value = 88% (161/18)

This was due to a particular viral infection which could also increase a little degree of C-reactive protein serum (Ruuskanen et al., 1985; Florman, 1985). Therefore, qualitative C-reactive protein serum examination has low diagnostic value and by itself cannot be used to maintain the diagnosis of bacterial meningitis.

In contrast to the C-reactive protein serum, there were eighteen out of 20 bacterial meningitis patients who had positive C-reactive protein cerebrospinal fluid. The outcomes of qualitative C-reactive protein examination of cerebrospinal fluid were 90% (18/20) sensitivity, 92% (20/24) specificity, 90% positive predictive value, and 92% negative predictive value (table 3).

Table 3 : *The outcomes of cerebrospinal fluid C-reactive protein examination of meningitis patients*

C-RP	Bacterial meningitis	Non bacterial meningitis	Total
Positive	18	2	20
Negative	2	22	24
Total	20	24	44

Sensitivity = 90% (18/20) Positive predictive value = 90% (18/20)
Specificity = 92% (22/24) Negative predictive value= 92% (22/24)

There was one out of 20 bacterial meningitis patients who had non milliarry tuberculous meningitis. According to De Beer et al. (1984) non milliarry tuberculous meningitis is only able to increase the level of light C-reactive protein serum. Therefore, the emergence of C-reactive protein in cerebrospinal fluid of non milliary tuberculous meningitis is still questionable. Moreover, in this investigation the cerebrospinal fluid C-reactive protein of tuberculous meningitis is imperative.

If tuberculous meningitis had been excluded from the study, the sensitivity and negative predictive value would have been higher (94.7% and 95.6% respectively), and would have increased the diagnostic value of cerebrospinal fluid qualitative C-reactive protein in non-specific bacterial meningitis. This was similar to some previous investigations (Corral et al., 1981; Mac Farlene and Narla 1985). Small samples in an investigation done by Walterspiele (1983) were probably the reason he got 60% sensitivity of the examination of cerebrospinal fluid qualitative C-reactive protein. Thus, examination of qualitative C-reactive protein of cerebrospinal fluid by means of latex agglutination slide test has high diagnostic value and can be used by clinicians to contribute maintaining the diagnosis of non-specific bacterial meningitis rapidly and accurately.

The mechanism of C-reactive protein emergence in the cerebrospinal fluid until now is still unclear. Passive diffusion process which is caused by the increase of brain barrier permeability due to some inflamation is suspectable. The diffusion of albumin and globulin serum through inflamed brain barrier has been proved (Krieg, 1979).

The average value of cerebrospinal fluid laboratory outcomes (amount of leucocyte, absolute polymorphonuclear, glucose and protein levels) between bacterial meningitis and non bacterial meningitis does not show prominent difference (table 4).

Table 4 : *The outcomes of cerebrospinal fluid laboratory examination of meningitis patients*

	AL cell/mm³	PMN cell/mm³	Glucose mg/ml	Protein mg/ml
Bacterial meningitis				
Range	100-5420	80-3766	6-80	75-999
Mean	1696	1016	39	235
SE	312	197	9	46
Non bacterial meningitis				
Range	0-2120	0-916	40-224	7-127
Mean	146	98	88	47
SE	85	75	10	9

When each of laboratory outcomes of cerebrospinal fluid was statistically examined and compared, the C-reactive protein had higher sensitivity and specificity. It can be concluded that the diagnostic value of qualitative C-reactive protein examination of cerebrospinal fluid is in the highest rank among other examinations (table 5).

Table 5 : *Sensitivity, specificity, positive and negative predictive values of cerebrospinal fluid*

	C-RP	AL 500/ mm³	PMN 250/ mm³	Glucose 40 mg/ dl	Protein 100 mg/ dl	Smear preparation
Sensitivity	90%	50%	75%	45%	80%	55%
Specificity	91%	87%	83%	91%	79%	100%
Positive predictive value	90%	77%	79%	88%	76%	100%
Negative predictive value	91%	68%	80%	66%	82%	69%

Sensitivity and specificity values of the amount of leucocyte, absolute polymorphonuclear, glucose and protein levels, and smear preparation were smaller compared to cerebrospinal fluid C-reactive protein in bacterial meningitis. It was because of the fact that 80% (16/20) of bacterial meningitis patients has already received early antibiotics before their admission and that influenced the amount of leucocyte, absolute polymorphonuclear, glucose and protein levels, and smear preparation of cerebrospinal fluid (Bell and Mc Cornick, 1981; Corral et al., 1981), and thus decreased the diagnostic value of those laboratory examinations.

Conclusion

Qualitative C-reactive protein of cerebrospinal fluid can be used as means to diagnose non-specific bacterial meningitis in children rapidly and accurately.

Suggestion

A further investigation on the use of cerebrospinal fluid C-reactive protein to diagnose tuberculous meningitis is needed.

REFERENCES

1. BELL, W.E.; MC CORMICK, W.F.: Neurologic infection in children; 2nd. ed. (W.B. Saunders, Philadelphia 1981).
2. CLARKE, D.; COST, K.; GAINESVILLE, F.L.A.; LOUSVILLE, K.Y.: Use of serum C-reactive protein in differentiating septic from aseptic meningitis in children. J.Pediat. 102 : 718–720 (1983).
3. CORRAL, C.J.; PEPPLE, J.M.; MOXON, E.R.; HUGHES, W.I.: C-reactive protein in the spinal fluid of children of meningitis. J.Pediat. 99 : 365–369 (1981).
4. DE BEER, F.C.; KIRSTEN, G.F.; GIE, R.P.; BEYERS, N.; STRACHAN, A.F.: Value of C-reactive protein measurement in tuberculous, bacterial, and viral meningitis. Arch.Dis.Child. 59 : 653–656 (1984).
5. FLORMAN, A.L.: Interlekuin 1 and monitoring of acute infections. Pediatr.Infect.Dis. 4 : 450–452 (1985).
6. GRAY, B.M.; SIMMONS, D.R.; BARNUM, S.; VOLANIKIS, J.E.: Quantitative levels of C-reactive protein in cerebrospinal fluid in patients with bacterial meningitis and other conditions. J.Pediat. 108 : 665–670 (1985).
7. KAISER, A.B.; MC GEE, Z.A.: Central nervous system infections; in Shoemaker, Thomson, Holbrook : The Society of Critical Care Medicine Textbook of Critical Care; ed...; pp... (W.B. Saunders, Philadelphia, London 1984).
8. KOMOROSKI, E.M.; HARE, G.V.; SHURIN, P.A.; VAHEY, J.B.A.; JOHNSON, C.: MORCHANT, C.D.M.; SCHILLIAN, J.: Quantitative measurement of C-reactive protein in acute otitis media. J.Pediat. 3 : 81–84 (1977).
9. KRIEG, A.F.: Cerebrospinal fluid and other body fluid, in Davidson, Henry: Todd Sanford's Clinical Diagnosis by Laboratory Methods, 16th ed..... pp..... (W.B. Saunders, Philadelphia, London 1979).
10. MAC FARLANE, D.E.; NARLA, V.R.: Cerebrospinal fluid C-reactive protein in the laboratory diagnosis of bacterial meningitis. Acta paediat. scand. 74 : 560–563 (1985).
11. MC CARTHY, P.L.; FRANK, A.L.; ABLOW, R.C.; MASTESS, S.J.; DOLAN, T.F.: Value of the C-reactive protein test in the differentiation of bacterial and viral pneumonia. J.Pediat. 92 : 454–456 (1978).
12. MC PHERSON, R.A.: Specific proteins, in Henry: Todd Sanford's Davidson Clinical Diagnosis and Management by Laboratory Methods, 17th ed..... pp..... (W.B. Saunders, Philadelphia, London, Toronto 1984).
13. PELTOLA, H.: C-reactive protein in rapid monitoring of infections of the control nervous system. *Lancet i* : 980–983 (1982).
14. PELTOLA, H.: C-reactive protein in rapid differentiation of a acute epiglositis from spasmodic croup and acute laryngocheitis. A preliminary report. J.Pediat. : 713–715 (1983).
15. PELTOLA, H.; LETHALA, K.; MALMORI, P.: C-reactive protein as a detector of organic complications during recovery from childhood purulent meningitis. J.Pediat. 104 : 869–872 (1984).
16. PEPYS, M.B.: C-reactive fifty years on *Lancet i* : 653–657 (1981).
17. PHILIP, A.G.S.; BAKER, C.J.: Cerebrospinal fluid C-reactive protein in neonatal meningitis. J.Pediat. 102 : 715–717 (1983).
18. PHILIP, A.G.S.: Respon on C-reactive protein in neonatal group B streptococcal infection. Pediatr.Infect.Dis. 4 : 145–148 (1985).
19. RUUSKANEN, O.; PUTTO, A.; SARKKINEN, H.; MEURMAN, O.; IRJALA, K.: C-reactive protein in respiratory virus infections. J.Pediat. 107 (1) : 97–100 (1985).
20. SABEL, K.G.; WADSWORTH, Ch.: C-reactive protein in early diagnosis of neonatal septicemia. Acta paediat. scand. 68 : 825–831 (1979).
21. SHAFFER, J.G.; GOLDEN, M.: Serodiagnostic test in diseases other than syphilis, in Davidson, Henry: Todd Sanford's Clinical Dignosis by Laboratory Methods; 14th ed. pp. (W.B Saunders, Philadelphia 1969).
22. SONNENWIRTH, A.C.: Miscellaneous serologic test: Gradwohl's Clinical Laboratory Methods and Diganosis; 7th ed., volume one; pp. (The C.V. Mosby, ... 1970).
23. SPEER, C.H.; BURNS, A.; GAHR, M.: Sequential determination of C-RP, X, antitrypsin and haptoglobulin in neonatal septicaemia. Acta pediat. scand. 72 : 679–683 (1983).
24. WALTERSPIEL, J.N.: C-reactive protein in cerebrospinal fluid. Pediatr.Infect.Dis. 2 : 174–177 (1983).