

ORIGINAL ARTICLE

Early Ditection of Central Nervous System Infection by C-reactive Protein Examination of Cerebrospinal Fluid

by

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Abstract

There are still many cases of bacterial meningitis in Indonesia. The highest morbidity rate are between 2 months until 2 years of age. The important factors that influence the success of treatment are early diagnosis and detection of the cause.

C-reactive protein (=CRP) could be found in the spinal fluid of meningitis patients.

The aim of this study is to judge the ability of CRP as a tool in making diagnosis as soon as possible wheter there is a bacterial infection of the central nervous system and to compare it with the result of the spinal fluid culture. Also to compare the ability of it a conventional or routine examination of the spinal fluid was done.

This was a prospective study on 30 chidren that were admitted in the child ward of Kariadi Hospital, Semarang during the first of April until the and of July 1990. The ages of the children were between one month until 14 years, with clinical symptoms such as fever, seizure and neurological disorders. CRP examination was done with Latex Agglutination method. The result of CRP examination on spinal fluid showed that the sensitivity was 91.6% , the specificity 94.4% , the positive prediction value 91.6% and the negative prediction value 94.4%.

As a conclusion, CRP examination of spinal fluid gives better results than the conventional or routine examination in distinguishing bacterial meningitis from non bacterial meningitis.

Introduction

Many cases of bacterial meningitis, could still be found in Indonesia. The highest morbidity rate are between 2 months until 2 years of age [1]. Its mortality in neonates is very high (65.75%), and in children it is around 15 - 25% . The survivors might be have persistent sequelae.

The important factors that influence the success of treatment the disease is early diagnosis and detection of the cause and also the sensitivity of the causing agent of the disease to chemotherapy or antibiotics.

To make an early diagnosis of bacterial meningitis is not so easy. Conventional examination of spinal fluid such as cell count, differential count of cell, glucose and protein levels as the early diagnostic tool that was commonly used, often gives

doubtly results, especially when antibiotic had been given before [3]. Spinal fluid culture although it could detect around 85% cases of bacterial meningitis, will take time. C-reactive protein examination of spinal fluid could be used as the parameter to distinguish bacterial meningitis from non bacterial meningitis. CRP is a sensitive , fast, easy and less expensive examination, that's why it could be used as an early diagnostic tool to decide the therapy of central nervous infections and whether or not it is caused by bacteria.

The aim of this study is to judge the ability of CRP examination as a tool in making an early diagnosis of a bacterial infection of the central nervous system, and to compare it with the results of spinal fluid culture.

Materials and methods

This was a prospective study, on thirty children that were admitted in child ward in Kariadi Hospital, Semarang ; during the first of April until the end of July 1990, which were suspected central nervous system infection, they were between one month until fourteen years.

The suspicion of infection in the central nervous system was based on the following clinical symptoms : fever, seizure, decreased consciousness, or others neurological disorders such as meningeal

sign, pathological reflexes, bulging of the fontanel (in babies).

An aseptic lumbal puncture was done to all cases to get spinal fluid. Three various examinations of the spinal fluid were :

- Conventional / routine examination
- Culture
- C-Reactive Protein (CRP) examination

Conventional/routine examination are included cells count, glucose and protein level. According to the criteria of conventional examination, the diagnosis of meningitis are : (Kempe, 1980).

Parameter	Meningitis	
	Non Bacterial	Bacterial
Cell count/ mm ³	10 - < 500	> 500
Glucose (mg%)	> 40	< 40
Protein (mg%)	< 125	> 125

Positive agglutination (level of dilution)	CRP concentration (mg / L)
1/5	6
1/10	12
1/20	24
1/40	48
1/80	96
1/160	192

The spinal fluid culture is a parameter that has the highest diagnostic value in determining bacterial meningitis, so it could be used as "gold standard" for the other examination. About 0.5 cc spinal fluid sample was filled in the bottle containing transport medium, then it was laboratory tested for bacterial culture.

C-Reactive Protein examination was performed by latex agglutination as the semiquantitative method. Rapi Tex CRP (Behring Institute) was used as the reagents. The spinal fluid was diluted to 1/5, 1/10, 1/20, 1/40, 1/80, and 1/160. The procedures of the examination were as follows :

- * Spinal fluid and the reagents are placed in room temperature
- * Spinal fluid is diluted with normal saline solution (1/5, etc)
- * A drop of spinal fluid is dripped on a deck glass
- * Add a drop of reagents on that deck glass, mix it carefully
- * Wait about 2-3 minutes, then look at the reaction: agglutination means a positive reaction repeat the examination with stronger diluted solution until it gives a negative result.

The semi quantitative equivalent value between level of dilution of positive agglutination and CRP concentration are :

Data analysis

A positive result of spinal fluid culture shows a definite diagnosis of bacterial meningitis, meaning that spinal fluid culture is a parameter with a highest diagnostic value and thus could be used as "gold standard" in comparison with the other examinations (CRP and conventional). The ability of CRP as diagnostic tool is determined by analyzing sensitivity, specificity, and positive and negative predictive values to the result of the culture. Conventional examination of spinal fluid such as cell count, glucose and protein levels ; are also analyzed in the same way.

Fisher exact probability test was used as statistical analysis.

Sensitivity and specificity of diagnosis :

Sensitivity of diagnosis = $\frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}}$; or
The total positive result of CRP or conventional examination compared to the total positive result of the culture.

Specificity of diagnosis = $\frac{\text{True Negative}}{\text{True Negative} + \text{False Positive}}$; or

The total negative result of CRP or conventional examination compared to the total negative result of the culture.

Positive and negative prediction value :
Positive prediction value = $\frac{\text{True Positive}}{\text{True Positive} + \text{False Positive}} \times 100\%$
= % pure positive from all positive results.

Negative prediction value = $\frac{\text{True Negative}}{\text{True Negative} + \text{False Negative}} \times 100\%$
= % pure negative from all negative results

Result

During April until July 1990, there were 30 cases included in the study, the ages were between 3 months 72 months, consisting of 20 boys and 10 girls.

The spinal fluid culture showed that 12 (40%) cases had a positive result or proven as bacterial meningitis, 18 (60%) cases had a negative result or meaning non bacterial meningitis. From the positive cultures the type of bacteria were 4 *Streptococcus pneumoniae*, 3 *Hemophilus influenzae*, 2 *Neisseria meningitidis*, 2 *Pseudomonas sp.* and 1 culture revealed *Salmonella sp.*

Conventional spinal fluid examination that was appropriate to the diagnosis of bacterial meningitis for total cells > 500/ml was found in 5 (16.6%) cases, glucose level < 40 mg% in 20 (66.6%) cases and protein level > 125 mg% were found in 10 (33.3%) cases (Table I).

Concerning CRP examination of spinal fluid, if 6 mg/L was used as a cut off point value 13 (43.3%) cases were positive, but if 12 mg/L was used, there were 12 (40%) positive cases (Table I).

In comparing the result of conventional and CRP examination to the result of the culture, by determining the sensitivity and specificity of diagnosis (Table 2), cell count had 41.6% sensitivity and 100% specificity ; the glucose level showed 91.6% sensitivity and 50% specificity and protein level showed 50% sensitivity and 77.7% specificity.

C-Reactive Protein examination of spinal fluid, whether the sensitivity and also the specificity gave high values, either of it showed 91.6% and 88.8% for 6 mg/L cut off point value ; 91.6% and 94.4% for 12 mg/L cut off point value.

By "Fisher exact probability test" , the difference of sensitivity and specificity of all parameters from conventional examination to the result of culture showed no significance ($p > 0.05$). By the same method, the difference of sensitivity and specificity of CRP examination to the result of culture were significant ($p < 0.05$), meaning that CRP examination could be used in differentiating significantly bacterial from non bacterial meningitis.

Discussion

In this study, gold standard of the diagnosis of bacterial meningitis was determined by the result of spinal fluid culture, as it had the highest diagnostic value or gave definite diagnosis.

The result of the bacterial culture showed that most of them were *Streptococcus pneumoniae*, followed by *Hemophilus influenzae*, *Neisseria meningitidis*, *Pseudomonas sp.* and *Salmonella sp.*

Komalarini et al. In Jakarta (1980) found that Hemophilus influenzae were the majority [10]; Peltola et al. (1984) also found Hemophilus influenzae as the majority cause [7]. Swartz (1965) and Finland (1977) found the cause of bacterial meningitis the same as the result of this study, consecutively S. pneumoniae, H. influenzae and N. meningitidis (11,12).

The spinal fluid cell count showed only 5 cases with a total cells $> 500/\text{mm}^3$, 10 cases had $< 10/\text{mm}^3$, and 15 cases $10 - 500/\text{mm}^3$. From 5 cases with cells $> 500/\text{mm}^3$, all of the culture showed a positive result (pure positive). There were 7 cases with cell count $< 500/\text{mm}^3$ but the culture showed a positive result (False negative). This condition was probably an early stage of infection or in accordance to the fact that there were 3 cases which had already got prior antibiotics. The sensitivity of diagnosis by this examination was 41.6% and the specificity 100%. Corall et al. found that the sensitivity was 74% and the specificity 94% [4]. So even though it was specific for bacterial meningitis, nevertheless it was not sensitive.

Corall et al. also showed that the total cell of spinal fluid in bacterial and non bacterial meningitis crossed over one to the other, the range were $46 - 15,300/\text{mm}^3$ for bacterial and $23 - 471/\text{mm}^3$ for viral infection.

Tuberculous meningitis may also has a cell count of around $250 - 500/\text{mm}^3$ (Corall, Kempe), it meaning that a total cell up to $500/\text{mm}^3$ is still not specific.

Clinical diagnosis by cell examination in spinal fluid would be more valuable if the type of cells were evaluated, which one is more dominant PMN or MN, to distinguish whether or not it is bacterial meningitis.

According to the sensitivity and specificity of conventional and CRP examination as compared to the results of the culture, it showed that CRP had a higher sensitivity and specificity.

CRP was found in 11 from 12 cases of bacterial meningitis, and in non bacterial meningitis cases it was found only 2 in out of 16 cases if the 6 mg/L cut off point value was used, and only 1 from 17 cases if the 12 mg/L cut off point value was used ($p < 0.05$).

Corall et al. (1984) found a sensitivity of 100% and a specificity of 94% by the same study [4]. By taking samples repeatedly, it was proved that CRP level in the spinal fluid increased earlier than the cells, and CRP was also still found in the patient with prior antibiotics while the cell examination gave uncertain result (4).

The mechanism as to why CRP could be found in the spinal fluid is still unknown.

The penetration of albumin and globulin serum into the brain barrier diffusely when it was inflamed, has been known already. The same mechanism with CRP might be considered.

Operational analysis of CRP examination of spinal fluid for bacterial meningitis by calculating the positive and negative prediction value, showed also high values meaning that the outcome of false positive and false negative were low.

Herman Kurniawan (1984) studied the cut off point value of CRP in the spinal fluid to distinguish bacterial non bacterial meningitis, and had found that the dilution of the spinal fluid until $1/20$ (equal to mg/L) had the best correlation with the diagnosis of bacterial meningitis [13].

This study also revealed that a 12 mg/L border gave the best result in making a diagnosis of bacterial meningitis.

Table I. The result of spinal fluid examination

Type of examination		Culture		Total	
		(+)	(-)		
R	Total cell	$> 500/\text{ml}$	5	0	5
O		$< 500/\text{ml}$	7	18	25
U					
T	Glucose	$< 40 \text{ mg } \%$	11	9	20
I		$> 40 \text{ mg } \%$	1	9	10
N					
E	Protein	$> 125 \text{ mg } \%$	6	4	10
		$< 125 \text{ mg } \%$	6	14	20
C	(a) 6 mg/L	$> 6 \text{ mg/L}$	11	2	13
R		$< 6 \text{ mg/L}$	1	16	17
P	(b) 12 mg/L	$> 12 \text{ mg/L}$	11	1	12
		$< 12 \text{ mg/L}$	1	17	18

Table II. Sensitivity and specificity of diagnostic of routine and CRP examination to spinal fluid culture

Examination	Sensitivity (%)	Specificity (%)
Cell count	5/12 (41.6) *	18/18 (100.0) *
Glucose	11/12 (91.6) *	9/18 (50.0) *
Protein	6/12 (50.0) *	14/18 (77.7) *
CRP 6 mg/L	11/12 (91.6) *	16/18 (88.8) *
CRP 12 mg/L	11/12 (91.6) *	17/18 (94.4) *

* $p > 0.05$ ("Fisher exact probability" test)

** $p < 0.05$

Table III. Positive prediction value and negative prediction value of routine and CRP examination to spinal fluid culture

Examination	Positive prediction value (%)	Negative prediction value (%)
Cell count	5/5 (100%)	18/25 (72%)
Glucose	11/20 (55%)	9/10 (90%)
Protein	6/10 (60%)	14/20 (70%)
CRP 6 mg/L	11/13 (84.6%)	16/17 (94.1%)
CRP 12 mg/L	11/12 (91.6%)	17/18 (94.4%)

Summary

1. Culture of spinal fluid which is used in making a definite diagnosis of bacterial meningitis or non bacterial meningitis, takes time, and delay in determining the diagnosis gives consequences not only postponing treatment but also other disadvantages.
2. Routine or conventional examination of the spinal fluid with often gives uncertain results.
3. C-Reactive Protein (CRP) examination of the spinal fluid with a semiquantitative an agglutination test could be performed easily and taken in a short time.
4. CRP examination of spinal fluid is a very sensitive and is a specific parameter in determining early diagnosis of bacterial meningitis.
5. CRP examination of the spinal fluid gave better results than routine or conventional examination in distinguishing bacterial and from non bacterial meningitis.

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