ORIGINAL ARTICLE

Role of CSF-CRP in Diagnosis of Acute Bacterial and Aseptic Meningitis in Children

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ABSTRACT

Background: In children bacterial meningitis is one the significant cause of mortality and morbidity in developed and underdeveloped countries. Patients with suspected bacterial meningitis need an emergency medical care but due to delayed and improper diagnosis there is high risk of poor prognosis. With early and effective diagnosis of the condition prognosis of disease can be improved.

Aim: To determine the role of cerebrospinal fluid C-reactive protein in diagnosis of acute bacterial meningitis in children and to compare the cerebrospinal fluid C-reactive protein in cases of bacterial and aseptic meningitis.

Methods: This cross sectional study was designed at the Department of Paeds Medicine, KEMU/Mayo Hospital Lahore. Using non-probability sampling we took a sample of 184 patients (92 patients in each group). After obtaining written consent, lumbar puncture was done under aseptic measures according to the standard protocol. Cerebrospinal fluid was examined by bacteriology laboratory of the Department of Paediatrics, Mayo Hospital Lahore. C-reactive protein was measured in cerebrospinal fluid by quantitative latex agglutination method.

Results: The mean age of patients in bacterial meningitis group was 27.09±35.39 months and in aseptic meningitis were 29.27±37.73 months. There were 108 (58.70%) males and 76(31.30%) females in this study. The cerebrospinal fluid C-reactive protein findings were positive in 87(94.6%) patients in bacterial group and only 6 (6.5%) in aseptic group. There was highly significant association of the cerebrospinal fluid C-reactive protein findings with clinical bacterial meningitis (p-value<0.001). The mean positive cerebrospinal fluid C-reactive protein in bacterial meningitis was 35.18±23.11 and in aseptic meningitis 6.77±11.37.

Conclusion: Through this study we found that cerebrospinal fluid C-reactive protein can diagnose acute bacterial meningitis where culture is not possible or feasible.

Keywords: Meningitis, role of CSF-CRP, cerebrospinal fluid

INTRODUCTION

Meningitis is the inflammation of the leptomeninges, which are layers of the tissue that surround the brain and spinal cord. Major cause of meningitis is infection with a microorganism, which can be bacterial, tubercular, viral, fungal or protozoal[1]. It occurs in people of all age groups, but young children and infants are more predisposed to this disease[2]. The differentiation between pyogenic (bacterial) and aseptic meningitis is very important in its treatment. Bacterial meningitis is life threatening disease that results from bacterial infection of meninges presenting with acute onset of fever, headache, altered consciousness, neck stiffness and other signs of meningeal irritation[3].

Meningitis is a significant problem in many areas of the world. In United States, it affects about 3 in 100,000 people. 2,500 cases of meningitis occur in United Kingdom, each year[2]. Epidemics of bacterial meningitis affected more than 400 million people living in 21 countries from Senegal to Ethiopia during era of 1995–2014 (African meningitis belt)[4]. In a study done in 12 countries (Pakistan, Bhutan, Bangladesh, Indonesia, India, North Korea, Maldives, Nepal, Myanmar, Sri Lanka, Timor- Leste and Thailand), for a period from 2000 to 2011, it was reported that the incidence of meningitis vary in different countries, which ranges from 18.3 to 24.6 /10^5 populations[4]. In Pakistan, mortality rate due to meningitis was found 12-15%, while it is 5% in developed countries[5]. US department of commerce published report in year 2004 on calculated extrapolations of prevalence and incidence statistics for Meningitis in Pakistan. They reported that 14,632 individuals suffered meningitis out of a population of 159, 196, 336[6].

The infection is associated with high risk of long term morbidity and acute complications[7]. The definitive diagnosis of the meningitis requires an analysis of cerebrospinal fluid (CSF), which often shows disturbed glucose level along with white blood cell (WBC) count and protein level[8]. C-reactive protein(C-RP) is acute phase protein and it was reported in 1930 by Tillett *et al*[9]. Most of the inflammatory diseases may cause detectable levels of C-reactive proteinin serum or different body fluids those are closely associated with the affected tissues[10,11]. The ability of C - reactive protein to discriminate between patients with bacterial and viral meningitis has been shown in several reports[12]. A meta-analysis also reported that the negative C - reactive protein test in either serum or cerebrospinal fluid can be useful with high probability to rule out bacterial meningitis[13,14,15]. On the other hand, the diagnostic use of cerebrospinal fluid C-reactive protein to differentiate aseptic meningitis and bacterial has been investigated in a very few studies[10,11]. Corrall CJ et al inferred that C-RP was positive in 100% of initial lumbar puncture cerebrospinal fluid samples with culture positive bacterial meningitis, as compared to 6% patients with aseptic meningitis. Cerebrospinal fluid C-reactive protein had a specificity of 94% with a sensitivity of 100% in detection of culture-proven bacterial meningitis[16]. The initial cerebrospinal fluid C-reactive protein level was much sensitive parameter to differentiate between both types of meningitis when it was compared with number of cerebrospinal fluid glucose concentration, cerebrospinal fluid protein level, cerebrospinal fluid leukocytes, absolute cerebrospinal fluid polymorpho nuclear leukocytes or Gram staining of cerebrospinal fluid[16]. Patel et al. used cerebrospinal fluid C-

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reactive protein as a basic tool to differentiate between bacterial meningitis from aseptic meningitis, results were encouraging with sensitivity and specificity as 83.3% and 87.5% respectively for Pyo-meningitis[3]. This study is designed, to determine role of cerebrospinal fluid C-reactive protein in acute bacterial meningitis.

MATERIALS AND METHODS

This cross sectional study was conducted in the

$$n = \frac{z^2_{1-\alpha/2}[P_1(1-P_1) + P_2(1-P_2)]}{d^2}$$

Department of Pediatric Medicine unit II, K.E.M.U./Mayo Hospital Lahore during 10th October 2015 and 10th April 2016. Sample size of 184 patients (92 patients in each group) was taken by using 90% confidence level 5% error margin and by taking the expected percentage of cerebrospinal fluid-C-reactive protein positivity in patients with bacterial meningitis as 96.87% and in non- bacterial meningitis as5.714%[11]. Non Probability purposive sampling technique was used.

P1=96.87%

P2=5.714%

Margin of Error=5% $Z^{1-\alpha/2}$=90%

Inclusion Criteria

1. Any child consistent with clinical case definition of meningitis was included.
2. Culture and stain proven case
3. Recovery of pus in Cerebrospinal fluid
4. Both Male and Female
5. Age: 2months – 12years

Exclusion Criteria: Congenital anatomical defects of Neural tube where the puncture for Cerebrospinal fluid is not possible; local infection, bleeding diathesis & tuberculous meningitis

Children presenting to the paediatric medical emergency or outpatient department of Mayo Hospital Lahore, during 6 months period (after approval of synopsis) and fulfilling inclusion and exclusion criteria, were enrolled for the study after obtaining informed consent from father/mother. Confidentiality of the data was maintained. Socio-demographic data (age and sex) of all children was collected. After obtaining written consent, lumbar puncture was done under aseptic measures according to the standard protocol. Cerebrospinal fluid was examined by bacteriology laboratory of the department of Paediatrics; Mayo Hospital Lahore. C-reactive protein was measured in cerebrospinal fluid by quantitative latex agglutination method. This test is an immunological reaction between C-reactive protein antisera (goat IgG anti-human C- reactive protein) bound to biologically inert latex particles and C-reactive protein in the test specimen i.e. cerebrospinal fluid. When cerebrospinal fluid containing greater than 4mg/L C-reactive protein is mixed with the latex reagent, visible agglutination occurs[11]. Cerebrospinal fluid culture and/or Gram stain was used as gold standard markers. Cerebrospinal fluid- C-reactive protein was then be evaluated against these gold standard parameters. The data was analyzed in SPSS version 20. Quantitative variables (age, cerebrospinal fluid findings and C-reactive protein level) were presented by using mean ± standard deviation for bacterial meningitis. Qualitative variables (gender, chief complains and diagnosis) was presented by frequency table and percentage for bacterial meningitis. Comparison of cerebrospinal fluid among cases and controls was done by using independent sample-test/ Man Whitney U Test. Positivity of cerebrospinal fluid-Protein was compared in both treatment groups by using Chi- Square test. Probability (P-value) $\leq$ 0.05 was taken as significant.

RESULT

The mean age of patients in bacterial meningitis group was 27.09±35.39 months and in aseptic meningitis were 29.27±37.73 months. The age distribution of children in the two groups was also statistically same among different categories (p-value= 0.972).

Table 1: Comparison of Age (years) in both study groups

Age	Meningitis	
	Group I	Group II
<12 months	50(54.3%)	53(57.6%)
1-4 years	20(21.7%)	19(20.7%)
4-8 years	18(19.6%)	16(17.4%)
8-12 years	4(4.3%)	4(4.3%)
Total	92(100%)	92(100%)
Mean±S.D (months)	27.09± 35.39*	29.27±37.73*

*P value=0.976 P value=0.972

*The S. D is larger than mean due to large variation in data, i.e., from 2 months to 144 months

Fig. 1: Age distribution of the patients

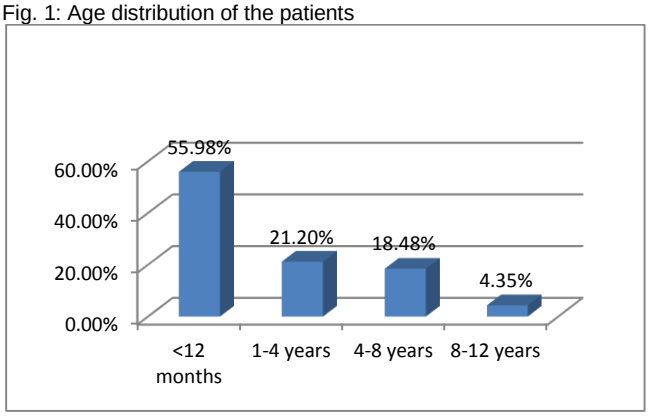

Table 2: Comparison of gender in both study groups

Age	Meningitis	
	Group I	Group II
Male	56(60.9%)	52(56.5%)
Female	36(39.1%)	40(43.5%)
Total	92(100%)	92(100%)

P value=0.549

Table 3: Comparison of cerebrospinal fluid findings in

	Meningitis	Mean	S.D	p-value
Glucose (mg/dl)	Group-I	38.65	13.88	<0.001
	Group-II	49.26	15.20	
Protein (mg/dl)	Group-I	72.79	28.68	<0.001
	Group-II	56.72	27.53	
TLC (cells/mm3)	Group-I	3689.09	2113.65	<0.001
	Group-II	253.78	269.95	
Neutrophils%	Group-I	76.2	71.12	<0.0001
	Group-II	18.33	22.91	
Lymphocytes (%)	Group-I	19.04	17.76	0.023
	Group-II	82.75	37.59	

Group-I (Bacterial Meningitis) and Group-II (Aseptic Meningitis)

Important cerebrospinal fluid findings were also compared in our study. The mean glucose level of patients in group-I

was 38.65±13.88 and in group-II was 49.26±152.20. The mean glucose level was statistically significant in the two groups (p-value<0.001). The mean protein of patients in bacterial group was 72.79±28.68 and in aseptic group was 56.72±27.53. The mean protein level was statistically significant in the two groups (p-value<0.001). The mean TLC level of patients in bacterial group was 3689.09±2113.65 and in aseptic group was 253.78±269.95. The mean TLC level was statistically significant in the two groups (p-value<0.001).

The mean neutrophils level of patients in group-I was 76.2±71.12% and in group-II was 18.33±12.91%. The mean neutrophils level was statistically significant in the two groups (p-value<0.001).The mean lymphocytes level of patients in bacterial group was 19.04±17.76% and in aseptic group was 82.75±37.59%. The mean neutrophils level was statistically significant in the two groups (p-value=0.023).

DISCUSSION

Meningitis remains a major cause of morbidity and mortality in younger age group in spite of the availability of bacterial vaccines. Reported cases of acute meningitis in children are mostly aseptic which usually do not require any specific therapeutic medications. About 5% of meningitis patients confines to pyogenic meningitis according to the literature and risk of severe neurological sequelae is increased with the delay in diagnosis and hence the treatment. Since the availability of vaccines in developed countries, burden of bacterial meningitis has reduced. Unfortunately, it still remains a major cause of life threatening infection, because of poor living conditions and limited resources available[29].

In U.S approximately 6000 new cases of pyogenic meningitis are reported each year. Out of these half of the infected patients are children younger than 18 years of age. S. pneumonia and N.meningitidis are the major causative agents of meningitis in children and associated with mortality rates of 6% to 12% and 3% to 5%respectively.

To distinguish between pyogenic and aseptic meningitis on clinical signs and symptoms is important in order to avoid unnecessary use of antibiotics and hospitalisations. However it is not possible all the time to distinguish between pyogenic and aseptic meningitis on clinical grounds. So, many clinicians recommend the immediate use of antibiotics in children on clinical suspicion of acute bacterial meningitis and to be continued for up to 72 hours until bacterial culture report arrives. As the consequences of delay in the diagnosis of bacterial meningitis can be life threatening, so a rapid and accurate diagnostic test is needed.

C–reactive protein levels have been used as rapid diagnostic tool in order to differentiate between pyogenic and viral infections in various clinical settings. Measurement of C-reactive protein levels has an important significance in the differential diagnosis of aseptic and pyogenic meningitis. Newly developed improved methods for the detection and quantification of C- reactive protein has enhanced its use in clinical medicine and made it an important diagnostic tool. Pakistan is a country with low socioeconomic strata and also facing the problems such as, poor healthcare facilities, lack of patient awareness etc. Hence, there is strong need to find a cheap, rapid and yet a reliable test for the early and correct diagnosis of pyogenic meningitis. Therefore, this study was conducted to determine role of cerebrospinal fluid-C-reactive protein in acute bacterial meningitis.

In our study, out of total184 patients, 103(55.98%) were less than 12 months old, 39(21.20%) were in 1-4 years of age category, 34(18-48%) were in 4-8 years and 8(4.35%) were in 8-12 years age category. The mean age of patients in bacterial meningitis group was 27.09±35.39 months and in aseptic meningitis were 29.27±37.73 months. The age distribution of children in the two groups was statistically same among different categories (p-value=0.972).There were 108(58.70%) males and 76(31.30%) females in this study. The gender distribution was statistically same among bacterial and aseptic groups (p-value= 0.549).

A study by Dubos *et al.* in 2008, identified the best biological marker for differentiating aseptic and pyogenic meningitis in children. In this study 198 patients were analysed, out of which, 96 were confirmed to have pyogenic meningitis. The mean age of patients with bacterial meningitis was 3.2±1.7 years with M/F of 0.9. Positive cerebrospinal fluid culture was seen in 76(38%) patients. The distribution of all blood and cerebrospinal fluid biological parameters differed significantly between patients with bacterial and aseptic meningitis. They reported a high odds ratio for all markers including C-reactive protein, cerebrospinal fluid, glucose, WBC and neutrophils however, the strongest of all was pro-calcitonin level.

In current study, the mean glucose level of patients in bacterial group was 38.65±13.88 and in aseptic group was 49.26±152.20. The mean protein of patients in bacterial group was 72.79±28.68 and in aseptic group was 56.72±27.53. Similar to above study, all noted parameters like glucose, protein,

Laboratory parameters such as cerebrospinal fluid routine analysis, blood cell indices and C- reactive protein level is assessed in children of age 3 months by a group of researchers in order to make differential diagnosis between bacterial and viral meningitis. The findings of the above mentioned study are comparable with our results showing significant differences in C - reactive protein levels between pyogenic and aseptic meningitis cases, while there is a big overlap in the rest of the two parameters. Nigrovic et al conducted a study on 696 children suffering with either pyogenic or aseptic meningitis, lead to the development of a simple multivariable model to distinguish aseptic meningitis from pyogenic meningitis. 18% of these patients were diagnosed with pyogenic meningitis and 82% had aseptic meningitis. The median age in derivation test was 5.00 months with range of 2.00-72.00 months.

CONCLUSION

1. This effective technique can help to differentiate bacterial and asepticmeningitis.
2. Determination of cerebrospinal fluid-C-reactive protein is rapid and cheap; on an average price, it costs PKR.500 whereas the culture costs PKR.1000 with a disadvantage of low yield.
3. Cerebrospinal fluid-C-reactive protein determination cuts the delay in initiation of antimicrobial therapy and

avoids unnecessary antibiotic exposure, so it is cost-effective.

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