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C - Reactive Protein and Bacterial Antigen in Childhood Meningitis.

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Abstract

Background: Meningitis may occur without warning in a perfectly normal infant or children, but there are a number of circumstances in which there is increased risk of the disease. Consequently, without proper medical treatment it carries a high mortality and morbidity. Estimation of CRP in serum and CSF as well as bacterial antigen in CSF will help to categories different types' meningitis which will help to select proper antimicrobial therapy. **Aim of the study:** The aim of the study was to determinate the CRP in serum and CSF as well as detection of bacterial antigen in CSF were studied in 40 cases of childhood meningitis to evaluate their diagnostic potential. **Methods:** This cross-sectional study was carried out in the Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Department of Immunology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic disorders (BIRDEM). Subjects were recruited randomly from the Department of Paediatrics, BSMMU, Department of Paediatric, Dhaka Medical College Hospital (DMCH) and Paediatric Medicine Unit, Dhaka Shishu (Children) Hospital during 1996 to 1997. A total 40 subjects clinically suffering from meningitis were selected randomly with inclusion and exclusion criteria.All data were analyzed by using SPSS program (SPSS for Windows, Release 7.5) and expressed as mean ± SD or in frequency or percentage unless mentioned otherwise. **Results:** A total 40 study subjects, a higher prevalence of meningitis was seen in the male patients in bacterial 12(30%) viral 11(27.5%) as well as female subjects 7(17.5%) found in both bacterial and tubercular group compared to4(10%) females found in viral and lowest 2(5%) male found in tubercular. Biochemical and cellular findings of CSF are also shown in table-V and figures 6-8. CSF glucose level (mg/dl, mean ± SD) was highest in viral group (52 ± 10) followed by control group (50±7), bacterial group (49±17) and tubercular group (44±9) and statistically there was significant difference among these groups (p = 0.016). Protein (mg/dl, mean ± SD) concentration in CSF was highest in bacterial group (223 ± 205) and lowest in tubercular group ((68 ± 38); whereas in control that was 106 ± 94 and in viral group 71 ± 56; there was statistical difference among these groups (p = 0.010). Cell type in CSF was predominantly lymphocyte in tubercular

Key words: CRP, CSF, Bacterial Antigen, Meningitis

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INTRODUCTION

Meningitis refers to an inflammation of the leptomeninges with infection of the cerebrospinal fluid within the subarachnoid space of the brain and spinal cord, and the ventricular system.[1] The disease in infants and older children is a serious clinical entity with signs and symptoms that commonly do not allow the physician to distinguish among the various etiological agents.[2,3] It may occur without warning in a perfectly normal infant or children, but there are a number of circumstances in which there is increased risk of the disease.[4] Meningitis may result in death within few days onset of disease.[5] Therefore, without proper medical treatment it carries a high mortality and morbidity.[5,6] Thus, prompt medical diagnosis is essential for initial empirical antibiotic therapy and general supportive management. Bacterial meningitis most commonly results from hematogenous dissemination of microorganisms from a distant site of inflammation.[2] The bacteremia either precedes it or occurs concomitantly. Bacterial colonization of nasopharynx with a pathogenic microorganism usually precedes the bacteremia.[2] A number of pathogens, bacterial or viral are commonly responsible for disease in childhood.[7] Bacteria which may produce pyogenic meningitis commonly includes Haemophilusin fluenzae, Streptococcus group B, Streptococcus pneumoniae, Neisseria meningitidis and Escherichiacoli.[8,9,10,11]

C-reactive protein (CRP), an acute-phase serum protein is a good indicator of local inflammatory activity and tissue damage. Elevation of CRP occur in many diseases including bacterial infections. Further, the duration and severity of infection, the type of tissue response or aseptic necrosis, genetic and ethnic variations, nutritional capacity of the liver may also influence the synthesis and secretion of CRP.[12] Hanson et al detected higher serum CRP level in all patients of bacterial meningitis included in his study.[13] Similarly, other investigators also have been observed to access the important diagnostic role of CRP in meningitis.[5,14] In tuberculous meningitis, the tissue response is chiefly mediated by T cells, macrophages along with few B cells and caseous necrotic tissue. These might be responsible for binding of larger quantities of CRP molecules, thereby permitting only a few of them to appear in CSF. This can be a probable explanation of undetectable level of CRP in CSF in tuberculous meningitis.[15] On the other hand, in pyogenic meningitis, the cells are mainly polymorphs lacking the sites for binding of CRP molecules which render CRP to be free in CSF and easily detectable. It is thus suspected that CRP level would vary among different subgroups of meningitis and may help in clinical categorization of these patients to institute rapid and appropriate therapy. Further to CRP detection in serum and CSF, culture of microorganism from CSF as well as detection of microbial antigens would strengthen critical differentiation of the variants of meningitis. These will clearly demarcate the variants of microorganism at least in pyogenic meningitis in context to age group involvement and selection of anti-microbial therapy. Moreover, when antibiotics are already administered, frequently culture becomes negative but still the microbial antigen remains prevalent in CSF.[2,16] On the other hand, serum is not a good specimen for

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detection of antigen as false positive reactions are common.[2,17]

It has been found that different organisms in meningitis affect different age groups. However, evaluation of bacterial antigens along with culture of CSF would better encompass the different categories of microbes involving meningitis, which would help in selection of specific antimicrobial therapy. The aim of the study was to determinate the CRP in serum and CSF as well as detection of bacterial antigen in CSF were studied in 40 cases of childhood meningitis to evaluate their diagnostic potential.

Objectives:

The study was conducted to estimate CRP level in serum and CSF of different etiologic groups of meningitis in children. And to evaluate the impact of bacterial antigen detection in CSF in the diagnosis of meningitis.

MATERIALS & METHODS

This cross-sectional study was carried out in the Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Department of Immunology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic disorders (BIRDEM). Subjects were recruited randomly from the Department of Paediatrics, BSMMU, Department of Paediatric, Dhaka Medical College Hospital (DMCH) and Paediatric Medicine Unit, Dhaka Shishu (Children) Hospital during 1996 to 1997. A total 40 subjects clinically suffering from meningitis. 10 age matched control subjects were collected irrespective of sex from the above institutions. Patients were selected randomly on their fulfillment of the set criteria. Recruitment was done on alternate weeks from Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka Medical College Hospital (DMCH) and Dhaka Shishu (Children) Hospital. On recruitment of each patient, a detailed history was taken from parents or guardians and thorough clinical examination was done. All data were collected in a prescribed data collection sheet as shown. Following the clinical examination 2 ml of blood was collected aseptically from the median cubital vein using a disposable syringe in a plain glass test tube. Blood was kept at room temperature to clot and centrifuged to separate serum within 2 hours. Serum of each patient was transferred to a microcentrifuge tube after labeling and preserved at -30°C until assay for the serum-CRP. Cerebrospinal fluid was also collected under highly aseptic method by performing lumber puncture. All lumber puncture were performed by Assistant Registrar of the respective institution. About 0.5 ml of CSF was collected in a previously autoclaved microcentrifuge tube.

It was labeled properly and preserved at -30°C until analysis for CSF-CRP and bacterial antigen test. For control subjects' serum and CSF was collected in the same way. Findings of routine test of blood and CSF were collected on the next visit. Patients continued their usual treatment as advised by the respective physician. A follow up was made and noted on another visit. Analysis of CRP in both serum and CSF and detection of bacterial antigen in the CSF were done in the Department of Immunology of BIRDEM. Whereas routine hematological test and cytology, biochemistry and bacteriology of the CSF were done in the

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department of pathology of the respective institution. C-reactive protein in both serum and CSF were estimated by using commercial kit. Bacterial antigen released in CSF was detected by using commercial sensitized bacterial antigen latex kit. All data were analyzed by using SPSS program (SPSS for Windows, Release 7.5) and expressed as mean ± SD or in frequency or percentage unless mentioned otherwise. Comparison between groups was done by analysis of variance (ANOVA), Chi-square, Kruskal Wallis 1-way ANOVA. Student's t-test, or Multivariate analysis, as applicable. Relationship among variables was calculated by Linear or Spearman's correlation. P value ≤ 0.05 was considered as the level of significance. For statistical calculation, if variable(s) of any patient was incomplete, that patient was dropped out from the specific group of patients for that calculation.

Inclusion criteria:

1. Children of age 1 month to 12 years of any sex with suspected meningitis.
2. Clinically positive meningeal signs irrespective of previous antibiotic therapy.
3. Children fit for age and who were neither suffering nor simulate features of meningitis.
4. Children who underwent lumber puncture for purpose other than meningitis.

Exclusion Criteria:

1. Age less than 1 month or more than 12 years.
2. Presence of any other systemic disease.
3. Recent history of trauma or surgery.

RESULTS

From a total 40 study subjects, a higher prevalence of meningitis was seen in the male patients in bacterial 12(30%) viral 11(27.5%) as well as female subjects 7(17.5%) found in both bacterial and tubercular. 4(10%) females found in viral and lowest 2(5%) male found in tubercular. 5(12.5%) both male and female found in control group [Figure-I].From the total of 40 cases of meningitis the mean±sd found from the age (months) of our study was 29±10 years in bacterial, 23±7 in viral, 59±13 in tubercular and 51±13 in control group [Table-I]. All the tubercular (100%) and most of the control subjects (90%) had past history of illness which were significantly higher (p = 0.0062) than bacterial (57.9%) and viral (33.3%) groups. History of respiratory tract infection was more common in bacterial group (68.4%) followed by tubercular (50%) and viral (40%) meningitis which was only 10% in control subjects (p = 0.0253). All the groups had statistically similar frequency of patients with drug history (p = 0.3321) [Table-II]. Hematological findings are shown in table V and figure 5. Hemoglobin level (gm/dl; mean ± SD) was 9.7 ± 1.7 in viral, 8.9 ±1.8 in control, 8.1±1.3 in tubercular and 7.8±1.8 in the bacterial group (p = 0.016). ESR (mm in 1st hour) is highest in tubercular (80±25), followed by bacterial (72±29), and similar in viral (38±26) and control (38 ± 14) groups (p = 0.000). Total count (p = 0.821), eosinophil (p = 0.314) and basophil (p = 0.806) count were statistically similar among the different groups, whereas polymorphs (p = 0.085) and lymphocytes (p = 0.068) reached border line significance for difference among different groups [Table-III].Biochemical and cellular findings of CSF are also shown in table-V and

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figures 6-8. CSF glucose level (mg/dl, mean ± SD) was highest in viral group (52±10) followed by control group (50 ± 7), bacterial group (49±17) and tubercular group (44 ± 9) and statistically there was significant difference among these groups (p = 0.016). Protein (mg/dl, mean ± SD) concentration in CSF was highest in bacterial group (223 ± 205) and lowest in tubercular group ((68 ± 38); whereas in control that was 106 ± 94 and in viral group 71±56; there was statistical difference among these groups (p = 0.010). Cell type in CSF was predominantly lymphocyte in tubercular group (83.3%), control group (70%) and in viral group (60%); whereas predominance in bacterial group was polymorphs (42.1%) and mixed cells (42.1%). There was again statistical difference among the four groups (p = 0.002) [Table-IV].

Level and status of CRP in serum and CSF are shown in table- V and VI. Serum CRP level (mg/liter, mean±SD) was highest in bacterial meningitis (142.74±45.82) which was 36.00±14.86 in tubercular group, 15,60±4.68 in viral group and 10.80 ± 9.54 in the control group and there was statistically significant difference among these groups (p = 0.0151). Similarly, CSF-CRP was also highest in bacterial group (11.37±2.70), followed by viral group (4.00 ± 1.80); and tubercular group (2.00 ± 1.30) and it was 0 (zero) in the control subjects. The level of significance for difference of CSF-CRP was p = 0.0044 among these four groups. Highest frequency of positive CRP in serum and CSF was observed in bacterial group, (94.7% and 78.9% respectively) and was lowest in the control group (20% and 0% respectively). The other two groups of viral (66.7% and 33.3% respectively) and tubercular (66.7% and 33.3% respectively) fall in between. CRP status in both serum (p = 0.0008) and CSF (p = 0.0004) showed significant difference among the four groups.

As shown in Table- VII, gram stain or stain for AFB was only positive in bacterial (31.6%) and tubercular (33.3%) cases. Accordingly, there was statistical difference among the four groups (p = 0.023). Showed in table-IX and figure 11 are the frequencies of positive bacterial antigen. All antigens were positive only in the bacterial group (Haemophilus influenzae 42.1%, p = 0.001: Streptococcus pneumoniae 21.1%, p = 0.069; neisseria meningitidis group B/Escherichiacoli Kl 5.3%, p=0.645 and neisseria meningitidis group C 5.3%, p=0.645). Table-VIII, show the association of gram stain, CRP and bacterial antigen with CSF culture in bacterial meningitis cases. No statistical difference was observed for gram stain (p = 0.911), serum CRP (p = 0.130) and CSF CRP (p = 0.750) with culture result. But it was significantly different for bacterial antigen (p = 0.007).Probable variables were age, history of respiratory tract infection, drug history, neurological deficit, total count, CSF cell count, CSF glucose, CSF protein, gram stain and AFB stain, CSF culture, CSF-CRP, serum CRP and bacterial antigen. For all the three factors of serum CRP (p = 0.000), CSF-CRP (p = 0.009) and bacterial antigen (p = 0.053), multiple regression showed significant relation between them. Further, in the case of serum CRP, drug history (p = 0.049), CSF protein (p = 0.001) and CSF-CRP (p = 0.018) were independent variables, whereas those for CSF-CRP were serum CRP (p = 0.018) and bacterial antigen (p = 0.098) and for bacterial antigen, they were drug history (p = 0.051), CSF glucose (p = 0.035) and CSF culture (p = 0.036).

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Correlations among the various parameters in different subject groups are shown in Table-XI. Serum CRP correlated with CSF-CRP in bacterial group (r = 0.652. p = 0.002), viral group (r = 0.805, p = 0.000) and tubercular group (r -0.766, p= 0.076); with CSF glucose in control group (r = -0.579, p = 0.079) only; CSF protein in bacterial group (r = 0.618, p = 0.005) and inversely in tubercular group (r = -0.814, p = 0.048), with duration of illness in bacterial group (r = 0.580, p = 0.009) but neither with CSF cell count nor ESR in any of the four groups. CSF-CRP correlated with protein in bacterial group (r = 0.424, p = 0.070) and in tubercular group (r = 0.768, p = 0.074), also nearly correlated with duration of illness in bacterial group (r = 0.429, p = 0.067). CSF glucose and protein correlated inversely in bacterial group (r = -0.671, p = 0.002). CSF cell count is inversely with CSF glucose in tubercular group (r = -0.825, p = 0.043) but with both CSF glucose (r = 0.435, p = 0.209) and CSF protein (r = 0.790, p = 0.006) in the control group. In the bacterial group CSF culture and bacterial antigen inversely correlated (r = -0.623, p = 0.004) but it did not correlate with gram stain nor with CSF cell count Bacterial antigen also did not have any significant correlation either with gram stain or with CSF-CRP or serum CRP.

Table- I: Gender distribution of the studied subjects (N=40).

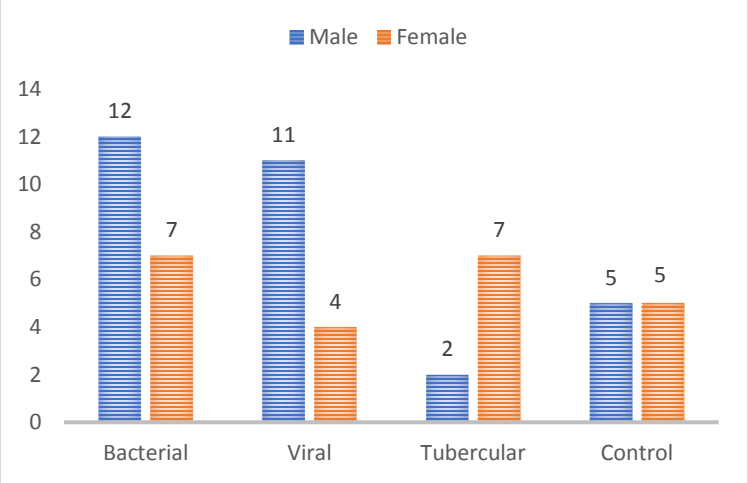

Table-I: Characteristics of the studied subjects (N=40)

Characteristics	Bacterial(n=19)	Viral(n=15)	Tubercular(n=6)	Control(n=10)	P
Age (months) mean ± SE	29 ± 10	23 ± 7	59 ± 13	51 ± 13	0.17
Neek rigidity (+ve / -ve)	16/3	11/4	5/1	3/7.	0.018
Kernig's sing (+ve / -ve)	16/3	11/4	5/1	3/7.	0.018

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Table- II: Clinical history in different meningitis subjects (N=40).

Variables	Groups				
	Bacterial(n=19)	**Viral(n=15)**	**Tubercular(n=6)**	**Control(n=10)**	**P**
H/O Past illness	11 (57.9)	5 (33.3)	6 (100)	9 (90.0)	0.0062
H/o Res. Tract infection	13 (68.4)	6 (40.0)	3 (50.0)	1 (10.0)	0.0253
Family H/O TB	0	0	2 (33.3)	0	0.0016
Drug history	8 (44.4)	8 (53.3)	3 (50.0)	8 (80.0)	0.3321
H/O Vaccination	16 (84.2)	11 (73.3)	1 (16.7)*	8 (80.0)	0.0126

Table-III: Haematological as well as biochemical and cellular findings of CSF in different types of meningitis (mean ± SD)

Character	Bacterial(n=19)	Viral(n=15)	Tubercular(n=6)	Control(n=10)	F/ χ^2	P
In blood						
Haemoglobinc (mg/dl)	7.8 ± 1.8	9.7 ± 1.7	8.1 ± 1.3	8.9 ± 1.8	3.795	0.016
ESR (mm in 1st hour)	72 ± 29	38 ± 26	80 ± 25	38 ± 14	8.642	0
Total count (/mm3)	11763 ± 2989	12807 ± 2259	13083 ± 2417	12670 ± 6875	0.306	0.821
Polymorphs (%)	66 ± 14	69 ± 20	51 ± 13	50 ± 21	2.351	0.085
Lymphocyte (%)	29 ± 13	38 ± 19	46 ± 13	44 ± 22	2.351	0.068
Esonphil (%)	3 ± 1	2 ± 1	2 ± 1	4 ± 3	1.218	0.314
Basophil (%)	1 ± 1	1 ± 1	0	1 ± 1	0.326	0.806
Monocyte (%)	3 ± 2	1 ± 1	2 ± 1	3 ± 3	2.488	0.072
In CSF						
Glucose (mg/dl)	44 ± 17	52 ± 10	49 ± 9	50 ± 7	3.808	0.016
Protein (mg/dl)	223 ± 205	71 ± 56	68 ± 38	106 ± 94	4.215	0.01
Predominant	8 (15.8)	0	0	0	25.811	0.002
Lymphocyte (%)	3 (15.8)	9 (60.0)	5 (83.3)	7 (70.0)		
Mixed	8 (42.1)	6 (40.0)	1 (16.7)	2 (20.0)		

Table-IV: CRP concentration (mg/liter, mean ± SE) in serum and CSF of various meningitis subjects.

Meningitis group	n	Serum CRP	CSF-CRP
Bacterial meningitis	19(47.5%)	142.74 ± 45.82	11.37 ± 2.70
Viral meningitis	15(37.5%)	15.60 ± 4.68	4.0 ± 1.80
Tubercular meningitis	6(15%)	36.00 ± 14.86	2.0 ± 1.30
Control	10(25%)	10.80 ± 9.54	0 ± 0
F		**3.8644**	**4.9945**
P		**0.0151**	**0.0044**
LSD		**89.53**	**5.95**

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Table-V: CRP status in serum and CSF in meningitis

Groups	n	Serum CRP		χ^2	CSF-CRP		x2
		+ ve	-ve	p	+ ve	-ve	p
Bacterial	19	18 (94.7)	1 (5.3)		15 (78.9)	4(21.1)	
Viral	15	10 (66.7)**	5 (33.3)	16.8473	5 (33.3)	10 (66.7)	18.2445
Tubercular	6	4 (66.7)	2 (33.3)	0.0008	2 (33.3)	4 (66.7)	0.0004
Control	10	2 (20)	8 (80)		0 (0)	10 (100)	

Table-VI: Status of gram stain/ Acid fast bacillus in CSF in different meningitis

Groups	n	Positive	Negative	χ^2& p
Bacterial	19	6 (31.6)*	13 (68.4)	9.534
Viral	15	0	15 (100)	0.023
Tubercular	6	2 (33.3)	4 (66.7)	
Control	10	0	10 (100)	

Table-VII: Positive bacterial antigen (H.influenzae, S. pneumoniae, Neisseria meningitis Group=A, Neisseria Meningitis Group-B,E.coliK1, Neisseria meningitidis Group-C) in different meningitis.

Groups	n	Haemophilus influenzae	Streptococcus pneumoniae	Neisseria meningitidis Gr-A	Neisseria meningitides Gr-B/E.coliK1	Neisseria meningitidis Gr-C
Bacterial	19	8 (42.1)	4 (21.1)	0	1 (5.3)	1 (5.3)
Viral	15	0	0	0	0	0
Tubercular	6	0	0	0	0	0
Control	10	0	0	0	0	0
χ^2	15.539	15.539	7.094		1.665	1.665
p	0.001	0.001	0.069		0.645	0.645

Table-VIII: Multiple regression analysis of serum CRP

ANOVA	Sum of squares	df	Mean square	F	P
Regression	643052.1	12	53587.68	5.944	0
Residual	234397.1.	26	9015.274		
Total	877449.2	38			

Variables	B	SE	Beta	t	p
Age	0.782	0.499	0.211	1.059	0.299
H/O Respiratory tract infection	69.327	51.12	-0.23	-1.356	0.18
Drug history	108.944	50.362	0.346	2.064	0.049

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Neurological deficit	28.811	57.627	0.074	0.5	0.621
Total count in PBF	0.003601	0.007	0.064	0.487	0.63
CSF cell count	-0.0217	10.017	-0.182	-0.1307	0.203
CSF Glucose	0.43	1.875	0.042	0.23	0.82
CSF Protein	0.583	0.153	0.0634	3.81	0.001
Gram stain & AFB stain	3.828	43.198	0.01	0.089	0.93
CSF culture	-30.424	46.787	-0.073	-0.65	0.521
CSF-CRP	5.334	2.108	0.0356	2.53	0.018
Bacterial antigen	39.586	53.161	0.124	0.745	0.463
Constant	173.611	163.93		-1.059	0.299

Table-IX: Multiple regression analysis of CSF-CRP

ANOVA	Sum of squares	df	Mean square	F	P
Regression	2272.654	12	189.388	3.024	0.009
Residual	1628.269	26	62.626		
Total	3900.923	38			

Variables	B	SE	Beta	t	p
Age	-0.0361	0.043	-0.143	-0.841	0.408
H/O Respiratory tract infection	-3.245	4.363	-0.162	-0.744	0.464
Drug history	1.558	4.518	0.078	0.345	0.733
Neurological deficit	4.193	4.755	0.161	0.882	0.386
Total count in PBF	0.000356	0.001	0.094	0.578	0.568
CSF cell count	-0.00193	-1	-0.242	-1.397	0.174
CSF Glucose	0.04716	0.156	0.069	0.302	0.765
CSF Protein	0.00291	0.016	0.047	0.183	0.856
Gram stain & AFB stain	-4.925	3.469	-0.199	-1.42	0.168
CSF culture	2.573	3.899	0.093	0.66	0.515
CSF-CRP	0.030705	0.015	0.556	2.53	0.018
Bacterial antigen	7.274	4.244	0.343	1.714	0.098
Constant	-5.181	13.917		-0.372	0.713

Table-X: Multiple regression analysis of Bacterial Antigen

ANOVA	Sum of	df	Mean	F	P
	squares		square		
Regression	3.308	12	0.276	4.544	0.053
Residual	0.303	5	6.07E+01		
Total	3.611	17			

Variables	B	SE	Beta	t	p

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Age	-1.69E-03	0.003	-0.168	-0.574	0.591
H/O Respiratory tract infection	-0.128	0.336	-0.135	-0.381	0.719
Drug history	-0.746	0.292	-0.827	-2.553	0.051
Neurological deficit	-7.29E-02	0.302	-0.051	-0.241	0.819
Total count in PBF	1.68E-02	0	0.112	0.436	0.681
CSF cell count	5.29E-05	0	0.215	0.824	0.447
CSF Glucose	-1.82E-02	0.006	-0.673	-2.872	0.035
CSF Protein	-1.05E-03	0.001	-0.474	-1.227	0.274
Gram stain & AFB stain	-0.24	0.176	-0.252	-1.36	0.232
CSF culture	-0.509	0.179	-0.536	-2.837	0.036
Serum-CRP	1.47E-03	0.001	0.655	1.557	0.18
CSF-CRP	-2.48E	0.008	-0.065	-0.318	0..764
Constant	2.027	0.624		3.248	0.023

Table-XI: Correlation

Determinants of ''r''	Bacterial		Viral		Tubercular		control	
	r	p	r	p	r	p	r	p
Serum-CRP vs. CSF-CRP	0.652	0.002	0.805	0	0.766	0.076		
Serum CRP vs CSF Glucose	-0.242	0.317	0.431	0.108	0.365	0.477	-0.579	0.079
Serum CRP vs CSF Protein	0.618	0.005	-0.002	0.994	-0.814	0.048	-0.376	0.284
Serum CRP vs CSF cell count	-0.111	0.65	-0.063	0.823	0.038	0.944	-0.454	0.188
Serum CRP vs ESR	0.179	0.462	-0.136	0.628	0.104	0.844	-0.0447	0.195
Serum CRP vs Elapsed time	0.58	0.009	0.167	0.552	-0.621	0.188		
CSF-CRP vs CSF Glucose	-0.258	0.286	0.149	0.597	-0.219	0.677		
CSF-CRP vs CSF Protein	0.424	0.07	-0.026	0.927	0.768	0.074		
CSF-CRP vs CSF cell count	-0.232	0.339	-0.124	0.569	0.538	0.271		
CSF-CRP vs ESR	0.191	0.433	0.018	0.949	-0.405	0.425		
CSF-CRP vs Elapsed time	0.429	0.067	0.26	0.349	-0.405	0.425		
CSF Glucose vs CSF Protein	-0.671	0.002	0.125	0.657	-0.115	0.828	0.065	0.858

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CSF Glucose vs CSF cell count	-0.129	0.599	-0.28	0.312	-0.825	0.043	0.435	0.209
CSF Protein vs CSF cell count	0.096	0.0695	0.058	0.837	-0.369	0.437	0.79	0.006
Gram stain vs CSF cell count	0.073	0.767						
Gram stain vs CSF cell culture	0.026	0.917						
Gram stain vs Bacterial antigen	-0.108	0.659						
CSF culture vs CSF cell count	-0.073	0.767						
CSF culture vs Bacterial antigen	-0.0623	0.004						
Bacterial antigen vs Serum CRP	0.314	0.19						
Bacterial antigen vs CSF-CRP	0.146	0.55						

DISCUSSION

The role of CRP estimation in serum and CSF as well as detection of bacterial antigen in CSF has been evaluated in this study for the diagnosis of childhood meningitis. In the present study, majority 19(47.5%) of the patients were having bacterial meningitis which was also observed in the early age group of childhood meningitis in another study in Bangladesh.[18] Respiratory tract infection (RTI) was found to be more common in the bacterial meningitis group (68.4%), followed by tubercular (50%) and viral group (40 %) in the present study. This may be due to the fact that following a respiratory infection some organisms persist in the body and at some stage cause meningitis.[2] In assessing the hematological findings, hemoglobin level and total count were not found to vary significantly between meningitis and non-meningitis as well as among the different groups of meningitis. Although differential count of lymphocytes was more among the patients of tubercular meningitis than to viral or bacterial meningitis (46% vs. 38 % or 26%), did it not vary between meningitis and non-meningitis control subjects. However, differential counts of polymorphs, eosinophil, basophil and monocyte did not have any significant variation between meningitis and non-meningitis as well as among different groups of meningitis patients. It was found that ESR was high both in meningitis and non-meningitis control subjects. ESR level was significantly higher in bacterial and tubercular meningitis compared to viral meningitis or non-meningitis patients and in tubercular meningitis ESR level was highest. Similar finding was also observed by another author.[4] In biochemical analysis of CSF, mean glucose level was found 44 ± 17 mg/dl in bacterial, 49 ± 9 mg/dl in tubercular and 52 ± 10 mg/dl in viral meningitis. A similar study by Converse et al. has also shown that glucose level in CSF was less than 45mg/dl in pyogenic meningitis

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and 45 mg/dl or more in aseptic meningitis.[19] CSF protein concentration was found to be significantly higher in bacterial meningitis compared to tubercular or viral meningitis. Raised protein concentration is due to increased permeability of blood brain barrier and also due to loss of albumin rich fluid from capillaries traversing the subdural space[2].Predominant cell type in CSF of tubercular meningitis patient was lymphocytes. Whereas in bacterial meningitis both polymorphs and a mixed type (polymorphs and lymphocytes) and in viral meningitis, lymphocytes and mixed type of predominant cells were found. These are also in agreement with the common findings in different type of meningitis.[20] Serum CRP level was found to be highest (142.74 ± 45.82 mg/liter) in children with bacterial meningitis. Although viral group showed a lower serum CRP level (15.6 ± 4.68 mg/liter) than tubercular group (36 ± 14.86 mg/liter), both of them had higher values than that of control subjects (10.8 mg/liter). In the present study, CRP level in CSF was higher in bacterial (11.37 ± 2.7 mg/liter) and viral group (4 ± 1.8 mg/liter) than tubercular group (2 ± 1.3 mg/liter). However, it was not detectable in CSF of the control group. It has been observed that. predominance of lymphocytes in CSF of tubercular meningitis might be responsible for utilization of CRP resulting in a lower CSF CRP level compared to the other groups.[15] As all the three groups of bacterial, viral and tubercular meningitis cases had elevated CRP level in CSF but undetectable CRP in control group, detection of CRP in suspected meningitis in CSF or a higher CRP level in serum would indicate diagnosis of meningitis. Both serum and CSF CRP levels correlated well in bacterial and viral meningitis ($r = 0.652$, $p = 0.002$, and $r = 0.805$, $p = 0.000$ respectively). CRP level in both serum and CSF positively correlated with duration of illness in the bacterial meningitis group.Test of bacterial antigen was found positive in most cases (14/19, 73.6%) of bacterial meningitis but microscopy after gram staining was found positive in only 6 cases (31.5%) and culture in 6 cases (31.5%). No false positive bacterial antigen was found in CSF from tubercular, viral or the control groups. Thus, the test for bacterial antigen could easily separate tubercular and viral from the bacterial meningitis group. Among these positive cases, bacterial antigen was highest for H. influenzae (42.1%) followed by S. pneumoniae (21.1%), N. meningitidis group-A / E coli (5.3%) and N meningitidis group-C (5.3%). It is worth mentioning that H. influenzae is the commonest causative organism of bacterial meningitis in the developing countries.[9,21]

In serum, bacterial antigen may give false positive results.[2,22] For example, bacterial antigen and CRP continue to circulate in blood and CSF even after early instillation of antibiotic in meningitis.[9,23] Bacterial antigen was positive only in pyogenic meningitis in the present study. This can easily separate tubercular and viral from bacterial group. No statistical difference was observed for gram staining, serum CRP and CSF CRP with culture, but the association of culture with bacterial antigen differed significantly. CSF culture inversely correlated with bacterial antigen in CSF in the bacterial group. It may be mentioned that antibiotic therapy (especially if given early) may interfere with culture finding.[24] This can be a factor in the present study that serum CRP level and bacterial antigen in CSF did not correlate with culture. Similarly, gram staining of CSF was only

positive in 6 cases (31.6%) of bacterial and 2 cases of tubercular meningitis (33.3 %) but not in viral and control subjects. Positive correlation of serum CRP with CSF CRP in all meningitis groups further emphasizes the impotence of CRP in the diagnosis of meningitis.

CONCLUSION

Serum CRP level was significantly raised in meningitis and it was found to be highest in bacterial meningitis followed by tubercular and viral meningitis. Moreover, CSF CRP was undetectable in control subjects although a high CRP level could be detected in CSF samples from children with bacterial, viral and tubercular meningitis. Thus, estimation of serum or CSF CRP level may be considered as an important laboratory tool for the diagnosis of meningitis. Detection of bacterial antigen in CSF sample showed no false positive results in tubercular or viral meningitis. A majority of the CSF samples of bacterial meningitis was found to be positive for bacterial antigen even in the absence of positive culture. Although serum CSF CRP was found to be useful in diagnosing meningitis and test for bacterial antigen in distinguishing bacterial meningitis from the other meningitis groups, it was found that other biochemical and cytological analysis of CSF sample were necessary for establishing the final diagnosis regarding the underlying cause. These findings suggest that CRP level in CSF and serum as well as bacterial antigen in CSF has got important value in early detection and management of meningitis in children.

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