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Role of CSF C- Reactive Protein in Rapid Diagnosis and Differentiation of Different form of Meningitis in Children

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Abstract **Original Research Article**

Background: Meningitis is a severe infection causing inflammation of the menengiase around the brain and spinal cord, primarily affecting infants, particularly neonates, leading to significant morbidity and mortality. ***Aim*****:** This study aimed to investigate the significance of CSF Creative protein in the early diagnosis of bacterial meningitis and to compare the sensitivity of CSF C-reactive protein in the diagnosis of bacterial meningitis with other parameters in order to differentiate between bacterial meningitis and other meningitis. ***Method*****:** A prospective cross-sectional study conducted at Benghazi Children's Hospital in a period from February 2022 to February 2023. A total of 100 children out of them 50 cases as case-control groups randomly selected recruited for this study. The age, gender and symptoms of the cases were determined. A blood test and detailed cerebrospinal fluid (CSF) analysis, including blood and CSF CRP levels, were done. ***Results*****:** The mean age of the study population was 9.12±5.89 months, ranging from 2 to 24 months. The mean age of meningitis cases was 7.42 ± 5.56 months. Almost half of cases fell in the age group (7–12) months. The distribution of cases with aseptic meningitis (27, 54%) was slightly higher than that with bacterial meningitis (23, 46%), totally; females (60, 60%) were more predominant than males (40, 40%). In bacterial meningitis cases, the female (14, 60.9%) gender was more predominant than male (9, 39.1%). All cases came with fever (27, 100%), and no cases came with convulsion (0, 00%), the mean level of CRP in blood was (199.13±59.31%), the level of CRP in CSF was (7.61±14.51), the mean concentration of white blood cell (WBC) in CSF was (219.48 ±161.76 x109/L)), the mean percent of neutrophils in CSF was (80±16.03%), the mean percent of lymphocyte in CSF (19.57±16.16)%), the mean concentration of sugar in CSF was (17.78±8.99mg/dl), the mean concentration of protein in CSF was (155.04±120.08mg/dl), and the mean count of red blood cells (RBC) in CSF was (nil) million/mm3. In bacterial meningitis, all the cases (23, 100%) had a sugar level less than two-thirds of blood sugar. Also, an equal number of cases accounting (11, 47.8%) each had a protein level in CSF greater than 45mg % and between 45-100 mg% respectively. In the CSF culture of bacterial meningitis, there was growth of bacteria in all cases (23, 100 %). The CRP in the CSF of aseptic meningitis cases was negative in nineteen cases (70.37%) and positive only in eight cases (29.63). The CRP in CSF was positive in all cases (23, 100%) with bacterial meningitis. In non-meningitis cases, the CRP in the CSF was negative in all cases (50, 100%). Sensitivity was 100%, specificity was 70.4%, positive predictive value was 74.2%, and negative predictive value was 100%. There was a significant difference in age distribution between meningitis and non- meningitis cases (P-value = 0.005). Nevertheless, there was no significant difference in age distribution between aseptic and bacterial meningitis cases (P-value = 0.708). There was no significant difference in gender distribution between meningitis and non- meningitis cases (P-value = 0.689) or between aseptic and bacterial meningitis cases (P-value = 0.247). There was a highly significant difference (P-value = 0.000) in the level of protein, the total count of WBC, and the level of CRP in CSF among meningitis and non-meningitis cases, except that sugar in CSF (mg/dl) was non- statistically significant (P-value = 0.108). There was a significant difference (P-value = 0.000) between C-reactive protein and individual CSF parameters in cases with different types of meningitis. ***Conclusion:*** The CRP levels in CSF offer high sensitivity and specificity. Therefore, the CSF- CRP can offer a valuable investigative method for differentiating bacterial from aseptic meningitis. It is a quick, sensitive, and reliable diagnostic test.

Keywords: Bacterial meningitis, viral meningitis, CSF, C-reactive protein.

INTRODUCTION

Meningitis is a severe infection in infants, especially neonates, with higher incidence in developed countries. Diagnosis is challenging due to overlap between biochemical analysis and cellular response, but early detection is crucial.

The pathologic bacteria involved in meningitis vary by vaccination state, recent trauma, and age.

Streptococcus pneumoniae and *Neisseria meniginitidis* are the most common organisms responsible for meningitis in adults, while *Listeria monocytogenes* is particularly common among the elderly. In neonates, *Streptococcus agalactia* and *Escherichia coli* are responsible for most meningitis. Viral meningitis is less severe compared to bacterial meningitis.

Bacterial meningitis is diagnosed through a positive CSF Gram stain and culture or bacterial antigen test, and patients with a compatible clinical presentation should be closely monitored for antibiotic therapy response. Viral meningitis, primarily caused by nonpolio enteroviruses, is the second major cause of meningitis, most common among young people and transmitted through various routes. Other viral agents include herpes simplex virus, varicellazoster virus, mumps virus, lymphocytic choriomeningitis virus, HIV, adenovirus, parainfluenza virus type 3, influenza virus, measles virus, and West Nile virus. Antiviral agents are available for HSV and VZV, but in most cases, only supportive measures are available for viral meningitis. Diagnosis involves various diagnostic methods, including CSF profile analysis, culture, microscopic examination, and targeted tests. CSF indices can help differentiate between different types of infections. Empiric therapy is used for bacterial meningitis, with antibiotics administered within 1 hour of hospital arrival, while viral meningitis patients can be treated at home with analgesics.

2. METHODOLOGY

2.1. Study Design

This was a prospective case series study conducted at Benghazi Children's Hospital in a period from February 2022 to February 2023. All children under 2 years old who full filling the definition of meningitis and underwent lumber puncture (LP) were included in this study.

2.1.1 Data collection

A total of 100 children case included in this study out of them 50 sample of case-control groups were randomly selected and recruited in this study. All cases were admitted with suspected meningitis symptoms in the period of study to both the intensive care unit (ICU) and other medicine wards units. Cases had received antibiotics and who had co-existing morbidities were excluded from the study. Based on CSF findings, and according to WHO case definition criteria (WHO, 1996), all patients were divided into the following groups:

- Bacterial meningitis (no = 23): Meningitis was defined as septic according to WHO case definition criteria: "children presenting with clinical symptoms of meningiti CSF with an elevated protein (>100 mg/dl) decreased glucose (100/mm3) with at least 80% neutrophils. Identification of bacteria directly by cultures were done.
- Aseptic meningitis (no = 27): Aseptic meningitis was defined as the presence of acute onset of meningitis symptoms WBC of > 5/mm3 of which > 50% were mononuclear/lymphocyte cells with the absence of any bacterial meningitis laboratory criteria.
- Control group (no = 50): The control group was defined by absence of inflammatory cells in CSF (WBC < 5/mm3) and sterile bacteriologic findings in afebrile children. As mentioned in Hrishi and Sethuraman. (2019) study, the type of WBC was lymphocytes, and the normal CSF Proteins and sugar were: 15–40 mg/dL and 50–80 mg/d (two thirds of blood glucose) respectively. The collected data included the following variables: age, gender, symptoms- reactive protein (CRP) level in blood, sugar level in blood red blood cell count (RBC), neutrophils percent, lymphocyte percent, sugar concentration, protein concentration, C-reactive protein (CRP) level, white blood cell count (WBC) in cerebrospinal fluid (CSF), and type of meningitis. The obtained data first compared between meningitis and non-meningitis groups and then compared between aseptic meningitis, bacterial meningitis and non-meningitis.

2.2 Laboratory methods

CSF samples collected by performing a lumber puncture by all aseptic techniques; after collection sent for CRP estimation, cytology, biochemistry, bacteriology, culture and sensitivity. Blood sample sent simultaneously to estimate CRP.

2.2.1 The procedure of C -reactive protein

It is a qualitative and semi-quantitative determination of C - reactive protein by agglutination to latex using AFINION™ CRP 1116787 (Abbott, USA). Normal reference of CRP in pediatric hospital is <0.6 mg/dl

2.3. Statistical analysis

The collected data, taken history, and the laboratory results of blood and CSF samples were coded, entered, double-checked, analyzed, and statistically presented using the software statistical package of social science (SPSS), version 22 (SPSS, Chicago, IL, USA). The selection of test was based on the normality of variables; the normal distribution was tested using the Shapiro-Wil k test. The qualitative data were presented as frequency table and percentages. The quantitative data were presented as mean±standard deviation (SD). The chi-square test was applied to investigate the association between categorical variables. The comparison of cerebrospinal fluid parameters among cases and controls was done by using independent sample-test/ Man Whitney U Test, and the comparison of cerebrospinal fluid parameters between different types of meningitis and control was done by using Kruskal-Wallis H test. A p value < 0.05 was considered statistically significant.

3. RESULTS

3.1 Age

3.1.1 Age distribution of study population

The mean age of the study population was (9.12±5.89) months, which ranged from 2 to 24 months. Totally, forty-one (41%) cases fell in the age group (2-6) months, then 38 (38%), 15 (15%) and 6 (6%) cases fell in the age groups (7-12), (13-18) and (19-24) months in decreasing order (Figure 1).

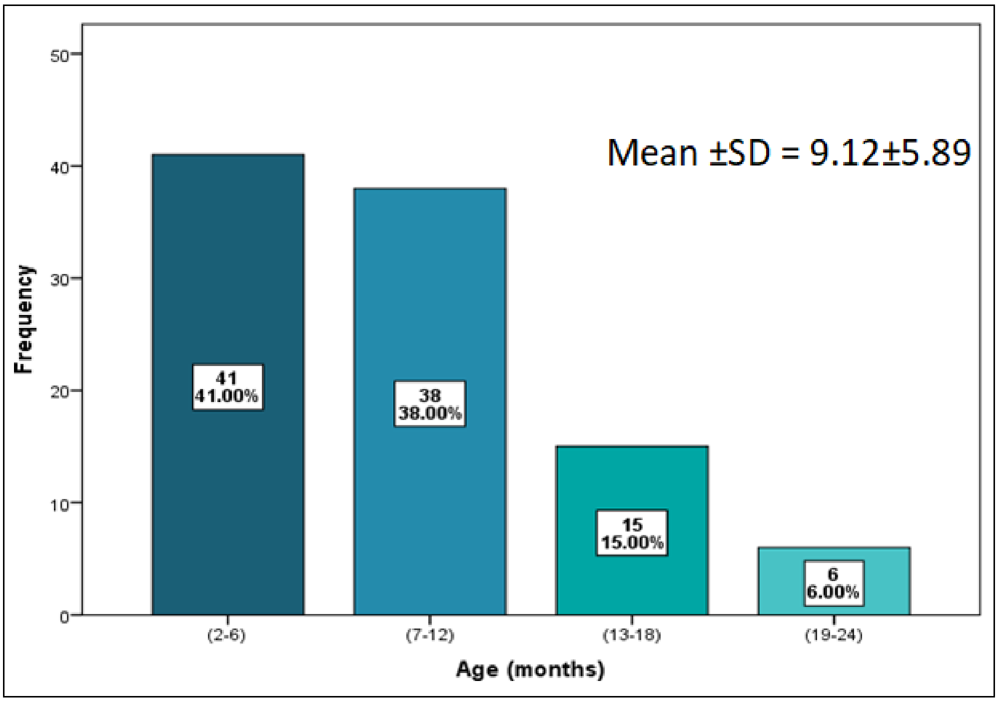

Figure 1: Age distribution of study population

The mean age of cases with meningitis was (7.42±5.56) months. In cases with meningitis, a few above half (29, 58%) of cases fell in the age group (2-6) months, fourteen (28%) of cases fell in the age group (7-12) months, six (12%) fell in the age group (13-18) and only one case (2%) fell in the age group (19-24) months. While, the mean age of non-meningitis cases was (10.82±5.76) months. Almost half of cases fell in the age group (7-12) months, twelve cases (24%) fell in the age group (2-6) months, nine (18%) and five (10%) cases fell in the age groups (13-18) and (19-24) months respectively. There was a statistically significant difference in age distribution between meningitis and non-meningitis cases (P-value<0.05, P-value=0.005) (Table 1**).**

Table 1: Age distribution of studied groups (n=100)

Age group (months)	Studied groups N (%)		P-Value
	Meningitis	Non-meningitis	
(2-6)	29 (58)	12 (24)	0.005*
(7-12)	14 (28)	24 (48)	
(13-18)	6 (12)	9 (18)	
(19-24)	1 (2)	5 (10)	
Total	50 (100)	50 (100)	
Mean±SD	7.42±5.56	10.82±5.76	

P-value from chi-square test، *significant result (P-value<0.05)

3.1.2 Age distribution according to types of meningitis

The distribution of cases with aseptic meningitis (27, 54%) was slightly higher than bacterial meningitis (23, 46%). In cases with aseptic meningitis, the number of patients in the age group (2-6) months was a few above half (15, 55.6%) months, seven patients (25.9%) fell in the age group (7-12) months, only four (14.8%) and one (3.7%) cases fell in the age groups (13-18) and (19-24) months respectively. In cases with bacterial meningitis, the biggest number (14, 60.9%) of patients was in the age group (2-6) months, seven cases (30.4%) fell in the age group (7-12) months, only two cases in age groups (13-18) months, and no cases were in the age group (19-24) months. In general, the distribution of aseptic and bacterial meningitis cases in different age groups was nearly comparable. There was no statistically significant difference of age distribution between aseptic and bacterial meningitis cases (P-value>0.05, P-value=0.708) (Table 2).

Table 2: Age distribution according to types of meningitis (n=50)

Age group (months)	Studied groups N (%)		P-Value
	Aseptic meningitis	Bacterial meningitis	
(2-6)	15 (55.6%)	14 (60.9%)	0.708
(7-12)	7 (25.9%)	7 (30.4%)	
(13-18)	4 (14.8%)	2 (8.7%)	
(19-24)	1 (3.7%)	0 (00%)	
Total	27 (54%)	23 (46%)	50 (100%)

P-value from chi-square test

3.2 Gender

3.2.1. Gender distribution of studied groups

Totally, females (60, 60%) were more predominant than males (40, 40%). In cases with meningitis, the distribution of males (24, 48%) and females (26, 52%) were nearly equal. In cases with no meningitis, the distribution of males (26, 52%) and females (24, 48%) were nearly equal. In general, the distribution of males and females between meningitis and non-meningitis was nearly compatible. There was no statistically significant difference in gender distribution between meningitis and non-meningitis cases (P-value>0.05, P-value=0.689) (Table 3).

Table 3: Gender distribution of studied groups100)

Age group (months)	Studied groups N (%)		P-Value
	Aseptic meningitis	Bacterial meningitis	
(2-6)	15 (55.6%)	14 (60.9%)	0.708
(7-12)	7 (25.9%)	7 (30.4%)	
(13-18)	4 (14.8%)	2 (8.7%)	
(19-24)	1 (3.7%)	0 (0%)	
Total	27 (54%)	23 (46%)	50 (100%)

P-value from chi-square test

3.2.2. Gender distribution according to type of meningitis

In aseptic meningitis cases, few above half (15, 55.6%) of cases were females and males were nearly half (12, 44.4%). Also, in bacterial meningitis cases, the female (14, 60.9%) gender was more predominant than the male (9, 39.1%) gender. There was no statistically significant difference in gender distribution between aseptic and bacterial meningitis cases (P-value>0.05, P-value=0.247) (Table 4).

Table 4: Gender distribution according to types of meningitis

Gender	Studied groups N (%)		P-Value
	Aseptic meningitis	Bacterial meningitis	
Male	15 (55.6%)	9 (39.1%)	0.247
Female	12 (44.4%)	14 (60.9%)	
Total	27	23	

Gender	Studied groups N (%)		P-Value*
	Aseptic meningitis	Bacterial meningitis	
Male	15 (55.6%)	9 (39.1%)	0.247
Female	12 (44.4%)	14 (60.9%)	
Total	27	23	

P-value from chi-square test

3.3. Clinical features

3.3.1 Distribution of symptoms according to type of meningitis and non- meningitis

The study found that in cases of aseptic meningitis, fever was the primary symptom, followed by poor feeding and irritability. In contrast, in cases of bacterial meningitis, fever was the primary symptom, with poor feeding and irritability being common in equal numbers. Convulsion was common in over three-quarters of cases. The study found a significant difference in the distribution of symptoms between aseptic and bacterial meningitis cases (P-value<0.05, P-value=0.000) (Table 5).

Table 5: Distribution of symptoms according to type of meningitis

Symptoms	Type of meningitis (50)		P-value
	Aseptic N (%) (n=27)	Bacterial N (%) (n=23)	
Fever	27 (100%)	23 (100%)	0.000*
Convulsion	0 (0%)	18 (78.3%)	
Poor feeding	16 (59.3%)	21(91.3%)	
Irritability	9 (33.3%)	21 (91.3%)	

3.4. The C-reactive protein and individual CSF parameters among cases with meningitis

In meningitis cases, the mean CRP level in the blood was 109.1±93.43%, while in the cerebrospinal fluid (CSF), it was 3.88±10.33. The mean concentration of white blood cells in CSF was 152.26±146.39, with a mean percent of neutrophils and lymphocytes at 47.80±32.15% and 51.80±32.21% respectively. The mean sugar and protein concentrations in CSF were 44.30±27.20 mg/dl and 96.36±98.68 mg/dl, respectively.

The study found a significant difference in C-reactive protein (CRP) levels in blood and cerebrospinal fluid (CSF) between cases of aseptic and bacterial meningitis. In aseptic cases, the mean CRP level was 32.41±14.03%, while in CSF, it was 0.7±0.20. The mean concentration of white blood cells in CSF was 95±104.13 x109/L. The mean percent of neutrophils and lymphocytes in CSF was 20.37±5.71%, 79.26±5.67%, and 66.89±13.17 mg/dl. The mean concentration of sugar in CSF was 66.89±13.17 mg/dl, and the mean protein concentration in CSF was 46.37±22.53 mg/dl. The mean count of red blood cells in CSF was nil million/mm3. The study concluded that there is a significant difference between C-reactive protein and individual CSF parameters and cases with aseptic and bacterial meningitis (Table 6).

Table 6: The C-reactive protein and individual CSF parameters among cases with meningitis

Parameters	Mean±SD			P-value
	Aseptic meningitis	Bacterial meningitis	Meningitis Total (50)	
CRP in blood	32.41±14.03	199.13±59.31	109.1±93.43	0.000*
CRP in CSF	0.7±0.20	7.61±14.51	3.88±10.33	0.000*
WBC($x10^9$/L) in CSF	95±104.13	219.48±161.76	152.26±146.39	0.003*
Neutrophils in CSF (%)	20.37±5.71	80±16.03	47.80±32.15	0.000*
Lymphocyte in CSF (%)	79.26±5.67	19.57±16.16	51.80±32.21	0.000*
Sugar in CSF (mg/dl)	66.89±13.17	17.78±8.99	44.30±27.20	0.000*
Protein in CSF (mg/dl)	46.37±22.53	155.04±120.08)	96.36±98.68	0.000*
RBC (million/mm^3) in CSF	nil	nil	nil	NC

P-value from independent sample-test/ Man Whitney U Test‹ *significant result (P- value<0.05), NC=Not calculated

3.4.1. The comparison of C-reactive protein and individual CSF parameters among studied groups

The study found a significant difference in the mean levels of CRP, WBC, sugar, and protein in CSF between meningitis and non-meningitis cases. The mean CRP level was 0.60±0.00, WBC was 1.28±1.50, sugar was 63.64±11.44 mg/dl, and protein was 24.76±8.15 mg/dl. However, the sugar concentration in CSF was non-statistically significant (Table 7).

Table 7: The comparison of C-reactive protein and individual CSF parameters among studied groups

Parameters	Studied group (Mean±SD) (100)		P-Value
	Meningitis (50)	Non-meningitis (50)	
CRP in CSF	3.88±10.33	0.60±0.00	0.000*
WBC($x10^9$/L) in CSF	152.26±146.39	1.28±1.50	0.000*
Sugar in CSF (mg/dl)	44.30±27.20	63.64±11.44	0.108
Protein in CSF (mg/dl)	96.36±98.68	24.76±8.15	0.000*

P-value from independent sample-test/ Man Whitney U Test‹ *significant result (P- value<0.05)

3.5. The comparison of sugar in CSF between studied groups.

In the study population, almost half of cases had sugar in the CSF less than two-thirds of the sugar in blood (47, 47%). The other few above half of cases had sugar in the CSF more than two-thirds of the sugar in the blood (53, 53%). In cases with meningitis, sixty percent of cases (30, 60%) had sugar in the CSF less than two-thirds of the sugar in the blood and the rest (20, 40%) of cases had sugar in the CSF more than two-thirds of the sugar in the blood. In non-meningitis cases, only one-third had sugar in CSF less than two-thirds of the sugar in the blood (17, 34%). Two-thirds of cases (33, 66 %) had sugar in the CSF more than two-thirds of the sugar in the blood. There was a statistically significant difference of sugar level in CSF between meningitis and non-meningitis cases (P-value<0.05, P-value=0.008) (Table 8).

Table 8: The comparison of sugar level in CSF between studied groups

Sugar in CSF	Studied groups N (%) (100)		Total	P-value
	Meningitis (50)	Non-meningitis (50)		
< 2 / 3 rd. of Blood Sugar	30 (60%)	17 (34%)	47 (47%)	0.008*
> 2 / 3 rd. of Blood Sugar	20 (40%)	33 (66%)	53 (53%)	
Total	50 (100%)	50 (100%)	100 (100%)	

P-value from chi-square test، *significant result (P-value<0.05)

3.5.1 The comparison of sugar in CSF between different types of meningitis and non-meningitis

In aseptic meningitis, one-quarter of cases (7, 26%) had a sugar level in CSF less than two-thirds of blood sugar, and almost three-quarters of cases (20, 74%) had a sugar level in CSF more than two-thirds of blood sugar. In bacterial meningitis, all the cases (23, 100%) had a sugar level less than two-thirds of blood sugar. There was a statistically significant difference of sugar level in CSF between the type of meningitis and non-meningitis cases (P-value<0.05, P-value=0.000) (Table 9).

Table 9: The comparison of sugar level in CSF between type of meningitis and non-meningitis

Sugar in CSF	Studied group N (%) (100)				P-Value
	Meningitis			Non-meningitis (50)	
	Aseptic (27)	Bacterial (23)	Total		
< 2 / 3 rd. of Blood Sugar	7 (26%)	23 (100%)	30 (60%)	17 (34%)	0.000*
> 2 / 3 rd. of Blood Sugar	20 (74%)	0 (0%)	20 (40%)	33 (66%)	
Total	27 (100%)	23 (100%)	50 (100%)	50 (100%)	

P-value from chi-square test، *significant result (P-value<0.05)

3.6. The comparison of protein in CSF between studied groups

In the study population, almost two-thirds (65, 65%) of cases had protein in CSF less than 45 mg% and the rest (24, 24%) and (11, 11%) had protein in CSF between 45-100 mg% and protein in CSF more than 100 mg% respectively. All the non-meningitis cases had protein in the CSF less than 45 mg%. In cases with meningitis, only fifteen cases (30%) had a protein level less than 45mg%, almost half of cases (24, 48%) had protein in CSF between 45-100 mg%, only eleven (22%) of cases had protein in CSF greater than 100 mg% (Table 10).

Table 10: The comparison of protein level in CSF between studied groups

Protein in CSF	Studied groups N (%)		Total	P-Value
	Meningitis	Non-meningitis		
< 45 mg%	15 (30)	50 (100)	65 (65)	0.000*
45 - 100 mg%	24 (48)	0 (00)	24 (24)	
> 100 mg%	11 (22)	0 (00)	11 (11)	
Total	50 (100)	50 (100)	100 (100)	

P-value from chi-square test, *significant result (P-value<0.05)

3.6.1. The comparison of protein in CSF between different types of meningitis and non-meningitis

In aseptic meningitis, no cases had protein level in CSF more than 100 mg %. While, nearly equal number of cases; (14, 51.9) and (13, 48.1%) had protein level in CSF less than 45mg% and between 45-100 mg% respectively. In bacterial meningitis, only one case had protein level in CSF less than 45mg %. An equal number of cases accounting (11, 47.8%) each had protein level in CSF more than 45mg% and between 45-100 mg% respectively (Table 11).

Table 11: The comparison of protein level in CSF between type of meningitis and non-meningitis

Protein in CSF	Studied group N (%) (100)			P-Value
	Meningitis		Non-meningitis (50)	
	Aseptic (27)	Bacterial (23)		
< 45 mg%	14 (51.9)	1 (4.3)	50 (100)	0.000*
45 - 100 mg%	13 (48.1)	11 (47.8)	0 (00)	
> 100 mg%	0 (00)	11 (47.8)	0 (00)	
Total	27 (100)	23 (100)	50 (100)	

P-value from chi-square test، *significant result (P-value<0.05)

3.7. The comparison of individual CSF parameters among different types of meningitis and non-meningitis

In aseptic meningitis cases, the mean concentration of sugar in CSF was (66.89±13.17) mg/dl), the mean concentration of protein in CSF was (46.37±22.53 mg/dl), the mean level of CRP in CSF was (0.70±0.20), and the mean concentration of white blood cell (WBC) in CSF was (95.00±104.13) (x109/L)). In bacterial meningitis cases, the mean concentration of sugar in CSF was (17.78±8.99 mg/dl), the mean concentration of protein in CSF was (155.04±120.08 mg/dl), the level of CRP in CSF was (7.61±14.51), and the mean concentration of white blood cell (WBC) in CSF was (219.48±161.76) (x109/L)). There was a statistically significant difference (P-value<0.05; P-value=0.000) between C-reactive protein and individual CSF parameters and cases with different types of meningitis (Table 12).

Table 12: The comparison of individual CSF parameters among different types of meningitis and non-meningitis

Parameters	Studied group (Mean±SD)			P-Value
	Meningitis		Non-meningitis (50)	
	Aseptic (27)	Bacterial (23)		
Sugar in CSF	66.89±13.17	17.78±8.99	63.64±11.44	0.000*
Protein in CSF	46.37±22.53	155.04±120.08	24.76±8.41	0.000*
CRP in CSF	0.70±0.20	7.61±14.51	0.60±0.00	0.000*
WBC($x10^9$/L) in CSF	95.00±104.13	219.48±161.76	1.28±1.50	0.000*

P-value from Kruskal-Wallis H test، *significant result (P-value<0.05)

3.8. The CSF culture results

3..81 The growth and type of bacteria grew in CSF culture of bacterial meningitis cases

All bacterial meningitis, samples showed growth of bacteria in all cases (23, 100%). There were nine types of bacteria grew in the CSF culture of all cases. The common types were *Klepsiella pneumoniae* (6, 26.1%), and *Streptococcus pneumoniae* (6, 26.1%), followed by *Staphylococcus aureus* (3, 13.1%), and *Streptococcus epidermidis* (3, 13.1%). The other five types grew in five cultures one for each case; *Actinobactor spp* (1, 4.3%), *Streptococcus hominis* (1, 4.3%), *Streptococcus viridans* (1, 4.3%), *Pseudomonas spp* (1, 4.3%), *Salmonella spp* (1, 4.3%) (Table 13).

Table 13: The type of bacteria grew in CSF culture of bacterial meningitis cases (n=23)

Organism	Type of bacteria	Frequency	Percent
Klebsiella pneumoniae	Gram positive	6	26.1
Staphylococcus aureus	Gram positive	3	13.1
Actinobactor spp.	Gram negative	1	4.3
Streptococcus pneumoniae	Gram positive	6	26.1
Streptococcus epidermidis	Gram positive	3	13.1
Streptococcus hominis	Gram positive	1	4.3
Streptococcus viridans	Gram positive	1	4.3
Pseudomonas spp	Gram negative	1	4.3
Salmonella spp	Gram negative	1	4.3
Total		23	100

3..82 C-reactive protein in CSF among studied groups

The C-reactive protein in the CSF of cases with aseptic meningitis was negative in nineteen cases (70.37%), and positive only in eight cases (29.63). Conversely, the C-reactive protein in CSF was positive in all cases (23, 100%) with bacterial meningitis. In non-meningitis cases, the C-reactive protein in CSF was negative in all cases (50, 100%). There was a statistically significant difference in CSF-CRP between aseptic and bacterial meningitis cases (P-value<0.05, P-value=0.000) (Table 14).

Table 14: C-reactive protein in CSF of studied groups (n=100)

CSF-CRP (mg/dl)	Studied group (Mean±SD)			P-Value**
	Meningitis		Non-meningitis (50)	
	Aseptic (27)	Bacterial (23)		
Negative (less than 0.6)	19 (70.37)	0 (00)	50 (100)	0.000*
Positive (more than 0.6)	8 (29.63)	23 (100)	0 (00)	
Total	27 (100)	23 (100)	50 (100)	

**p-value from chi-square test، *significant result (P-value<0.05)

3..83 Sensitivity and specificity for cerebrospinal fluid C-reactive protein in cases of meningitis

Sensitivity was 100%, specificity was 70.4%, and positive predictive value was 74.2% and negative predictive value 100%. Among 23 culture positive cases, 23 children (100%) had CSF CRP positivity (sensitivity 100%), and 27 culture negative cases, 19 children were negative for CSF CRP (specificity 70.4%). Out of the 31 children who showed CSF CRP to be positive, 23 also had some organisms grown in their CSF culture (Positive predictive value 74.2%) and CSF culture was negative for 19 children among the 19 children who tested to be CSF CRP negative (Negative predictive value 100%). Overall accuracy was 84% (42 / 50) (Table 15).

Table 15: Sensitivity and specificity for cerebrospinal fluid C-reactive protein in cases of meningitis

CRP	Culture N (%)		Total
	Negative	Positive	
Negative	19	0	19
Positive	8	23	31
Total	27	23	50

4. DISCUSSION

Meningitis diagnosis is based on history, physical examination, and CSF laboratory findings. Bacterial meningitis is a common serious illness during infancy and childhood, causing mortality and morbidity in children. Early recognition and treatment with appropriate drugs are crucial to avoid this situation. In this study, the age range of children ranged from 2 months to 2 years, as the lumbar puncture was restricted to cases in this age range. Studies have shown that both bacterial and non-bacterial involvement in meningitis is common in infancy, increasing the dependency on investigations for differentiation. The distribution of cases with aseptic meningitis (54%) was slightly higher than bacterial meningitis (46%), as per Malla *et al.*, (2013) study. However, the distribution of viral meningitis (34, 33%) was slightly higher than bacterial meningitis (32, 31.1%), therefore early recognition and treatment with appropriate drugs are crucial to avoid complications in children with meningitis. Ghuneim *et al.*, (2016) found that most children's meningitis cases are aseptic, caused by enterovirus. Despite the lack of specific treatment, most patients recover on their own. Natani *et al.*, (2017) classified cases based on CSF cytology, biochemistry, and bacteriology into three groups: bacterial meningitis (48 cases), aseptic meningitis (42 cases), and no meningitis (30 cases). However, our study found that viral meningitis cases were slightly lower. The study found that the distribution of aseptic and bacterial meningitis cases in different age groups was nearly comparable, with no significant age difference observed between viral and bacterial meningitis cases. This was consistent with previous studies by Abro *et al.*, (2008) and Águeda *et al.*, (2013). However, the study found that bacterial meningitis (BM) was evenly distributed in all age groups, while viral meningitis (VM) was more frequent among children over 12 months. Females were more predominant than males in this study, which differed from previous studies by Natani *et al.*, (2017) and Bansal *et al.*, (2021). In Bansal *et al.*,'s study, male numbers were slightly higher than females in the control group (normal CSF), but the difference was not statistically significant. Lee *et al.*, (2020) study showed that 61.4% of non-meningitis cases were male infants, and 64.9% of meningitis cases were male infants. In both aseptic and bacterial meningitis cases, females were higher than males, which differed from previous studies by Bansal *et al.*, (2021), which found higher male numbers in non-pyogenic meningitis and higher male numbers in pyogenic meningitis. In this study, there was no statistically significant difference in gender distribution between aseptic and bacterial meningitis cases, similar to Nadeem *et al.*, (2018) findings. Bansal *et al.*, (2021) study found that fever was common in all groups of meningitis, including non-pyogenic and pyogenic cases. Convulsions were common in almost half of non-pyogenic cases and in a few above half of pyogenic cases. This study found that all cases had fever, including aseptic and bacterial cases. However, the distribution of convulsions was different. Aseptic cases had no convulsion, while over three-quarters of bacterial cases had convulsions. Current results were not comparable to Kalpana's (2008) study, which found fever in the majority of pyogenic cases and fever in only half of non-pyogenic cases. Seizures were common in almost all cases of both pyogenic and non-pyogenic meningitis. The mean C-reactive protein and individual CSF parameters showed that bacterial meningitis cases had a higher mean CRP level in blood than aseptic cases. The study found that the mean CRP level in CFS in aseptic meningitis, bacterial meningitis, and control cases was lower than in bacterial meningitis. This is consistent with previous studies by Malla *et al.*, (2013), Bansal *et al.*, (2021), and Bansal *et al.*, (2013). The mean CRP level in the CFS was significantly higher in bacterial meningitis cases than in viral meningitis cases. The mean CRP concentration in CFS of non-meningitis cases was also lower (0.6±0.00) than in meningitis cases (3.88±10.33). These results are consistent with previous studies by Mayah *et al.*, (2013) and Lee *et al.*, (2020), which found lower CRP concentrations in the CSF of non-meningitis cases. The difference in CSF CRP between bacterial and all other groups was highly significant, with bacterial meningitis having the highest CRP mean value. The study also found that the mean concentration of CRP in CFS of non-meningitis cases was lower than in meningitis cases (3.88±10.33) and higher than in meningitis cases (24.32±33.66 ×103 (/µL)). This study analyzed the mean concentration of white blood cells (WBC) in cerebrospinal fluid (CSF) in cases of bacterial meningitis, aseptic meningitis, and non-meningitis cases. The results showed that bacterial meningitis cases had the highest mean WBC count, followed by aseptic meningitis cases and control cases. Malla *et al.*, (2013) found that the mean total count in CSF of cases with bacterial meningitis was higher than in cases with viral meningitis. The non-meningitis cases had the lowest mean level of total count in CSF (0.1081 ± 0.458). The mean WBC count was significantly higher in patients with BM (mean, 4839 cells/L) compared to patients with VM (mean, 159 cells/L), with those with AM (mean, 577 cells/L), and both ($p < 0.001$). These results were consistent with the study results. In non-meningitis cases, the mean concentration of WBC was lower (1.28±1.50) (x109/L) than in meningitis cases (152.26±146.39 (x109/L). This difference was not comparable to the results of Ghuneim *et al*., (2016) study, which found the mean percent of neutrophils in CSF of cases with bacterial meningitis was lower (51±30) than in cases of aseptic meningitis (52±19). Malla *et al.,* (2013) found that the mean percent of neutrophils in the CSF of cases with bacterial meningitis was much higher (84.18±12.26) than in cases of viral meningitis (10.88 ± 11.57). The study found that the mean percentage of lymphocytes in the cerebrospinal fluid (CSF) of cases with bacterial meningitis was significantly lower than in cases with aseptic meningitis (79.26±5.67%). This finding is consistent with previous studies by Malla *et al.,* (2013) and Ghuneim *et al.,* (2016), who found similar results. The mean percentage of neutrophils in the blood of cases with bacterial meningitis was also higher than in cases with viral meningitis. Nadeem *et al*., (2018) also found lower lymphocyte percentages in the blood of cases with bacterial meningitis. The mean concentration of sugar in CSF of aseptic meningitis cases, bacterial meningitis, and no meningitis cases was also lower. The mean glucose level in CSF of patients with bacterial meningitis was also lower than in the aseptic group. These findings align with previous studies by Bansal *et al.,* (2021), and Mayah *et al*., (2013), which found similar results in glucose levels in CSF for pyogenic meningitis, non-pyogenic meningitis, and normal CSF. The study found that the mean protein concentration in the cerebrospinal fluid (CSF) of aseptic meningitis, bacterial meningitis, and non-meningitis cases was significantly higher than those in Bansal *et al.*, (2021) work. Bacterial meningitis cases had the highest mean protein level, while non-meningitis cases had the lowest. Malla *et al.,* (2013) study showed that the mean protein level in CSF of bacterial meningitis cases was significantly higher than that of viral meningitis cases. The non-meningitis cases had the lowest mean protein level. Similarly, Mayah *et al.,* (2013) results showed that the mean protein level in CFS in aseptic meningitis, bacterial meningitis, and control cases was significantly higher than those in viral meningitis cases. Nadeem *et al.*, (2018) and Ghuneim *et al.,* (2016) studies found that the mean protein level in CSF of bacterial meningitis cases was significantly higher than in viral meningitis cases. Abro *et al.*, (2008) study found that the CSF protein level was significantly higher in bacterial than viral meningitis patients were. The study found a significant difference in C-reactive protein, CSF parameters, and meningitis cases among cases, similar to Bansal *et al*., (2021) findings that showed a significant difference in WBC count, glucose, and protein levels in CSF among pyogenic meningitis, non-pyogenic meningitis, and normal CSF (p-value < 0.05). Malla *et al*., (2013) found a significant difference in CSF parameters, meningitis types, and control groups. Lee *et al.,* (2020) found no significant difference in WBC and CRP levels between meningitis and non-meningitis groups. The study found that cases had less sugar in CSF and more than two-thirds sugar in blood were nearly equal. Aseptic meningitis had a lower sugar level in CSF than blood sugar, and bacterial meningitis had lower lymphocytes in CSF than viral meningitis. The study reveals that the mean percentage of lymphocytes and neutrophils in the CSF of cases with bacterial meningitis is significantly higher than that of cases with viral meningitis. This contrasts with previous studies, which found similar percentages of lymphocytes and neutrophils in both cases. Additionally, the mean concentration of sugar in the CSF of aseptic meningitis cases, bacterial meningitis, and no meningitis cases was significantly lower. These findings highlight the importance of understanding the differences between these studies. The mean sugar concentrations in cerebrospinal fluid (CSF) of aseptic meningitis cases was higher than bacterial meningitis cases, according to a study by Ghuneim *et al*., (2016). This finding is consistent with previous studies by Nadeem *et al*., (2018), Bansal *et al*., (2021), and Mayah *et al*., (2013), which found that the mean glucose level in CSF in pyogenic meningitis, non-pyogenic meningitis, and normal CSF was 64.81±5.58 mg/dl. The study also found that the mean glucose level in CFS in aseptic meningitis, bacterial meningitis, and control cases was 51.5±11.68 mg/dl, 25.6±8.4, and 53.6±13.3, respectively. The study found that the mean protein concentration in the cerebrospinal fluid (CSF) of aseptic meningitis, bacterial meningitis, and non-meningitis cases was significantly higher than that of Bansal *et al*., (2021) and normal CSF. Bacterial meningitis cases had the highest mean protein level, while non-meningitis cases had the lowest. This finding is consistent with previous studies by Malla *et al*., (2013), Mayah *et al*., (2013), Nadeem *et al*., (2018), and Ghuneim *et al.,* (2016), which found that the mean protein level in CSF of cases with bacterial meningitis was significantly higher than in cases with viral meningitis. The mean protein of patients in the bacterial group was also higher than in the aseptic group. These findings are consistent with previous studies by Nadeem *et al*., (2018) and Ghuneim *et al*., (2016). The study found a significant difference in C-reactive protein, individual CSF parameters, and cases with different types of meningitis in our cases, similar to Abro *et al.*, (2008) findings. This was also similar to Bansal *et al*., (2021) findings, which found a significant difference in total WBC count, glucose, and protein levels in CSF among pyogenic meningitis, non-pyogenic meningitis, and normal CSF. Malla *et al.* (2013) study also found a significant difference between different CFS parameters, types of meningitis, and control groups. A study done by Lee *et al*., (2020) found no significant difference in WBC and CRP levels between meningitis and non-meningitis groups. The comparison of sugar in CSF between study populations showed that cases had less sugar and more than two-thirds sugar in blood were nearly equal. In aseptic meningitis, one-quarter of cases (7.26%) had a sugar level in CSF less than two-thirds of blood sugar, while almost three-quarters (20.74%) had a sugar level more than two-thirds of blood sugar. In bacterial meningitis, all cases (23, 100%) had a sugar level less than two-thirds of blood sugar. These results were similar to the results of Kalpana's (2008) work, which found that only 30% of cases had a sugar level less than two-thirds of blood sugar, and 70% had a sugar level greater than two-thirds. The study also found that almost two-thirds (65%) of cases had protein in CSF less than 45 mg%, while the rest (24, 24%) and (11, 11%) had protein in CSF between 45-100 mg% and more than 100 mg%, respectively.

Current study found that protein levels in the CSF of non-meningitis cases decreased with increasing protein levels, in line with Kalpana's (2008) findings. The majority of cases had protein levels below 45 mg%, while 34% and 11% had protein levels between 45-100 mg% and more than 100%, respectively. In the current study, all non-meningitis cases had protein levels less than 45 mg%. In aseptic meningitis, nearly equal numbers of cases had protein levels less than 45 mg% and between 45-100 mg%, respectively. In bacterial meningitis, only one case had a protein level less than 45 mg%, while 47.8% had protein levels greater than 45 mg% and between 45-100 mg%. The results differed from the Kalpana (2008) study, which found that 80% of non-pyogenic meningitis cases had protein levels below 45 mg%, 14% had protein levels between 45 and 100 mg%, and 6% had protein levels more than 100 mg%. In pyogenic meningitis, protein levels were less than 45 mg% in 30% of cases, between 46 and 100 mg% in 54%, and more than 100 mg% in 16% of cases. In CSF culture of bacterial meningitis, growths of bacteria were found in all suggestive cases (23, 100%).

The study found that nine types of bacteria grew in the CSF culture of all cases, with *Klepsiella pneumoniae* (26.1%) and *Streptococcus pneumoniae* (6.1%), followed by *Staphylococcus aureus* (3.1%), and *Streptococcus epidermidis* (3.1%). These results differ from previous studies, such as Abro *et al.*, (2008), which found *Meningococci spp* in 36 cases, *Streptococcus pneumoniae* in 22 cases, *Staph. aureus* in two, *Klebsiella pneumoniae* in two, *Streptococcus agalactiae* in one, and *E. coli* in one patient in 22 patients, no organism was isolated, but CSF changes were suggestive of bacterial meningitis, and these patients were treated with antibiotics.

The C-reactive protein in the CSF of cases with aseptic meningitis was negative in nineteen cases (70.37%) and positive only in eight cases (29.63). In contrast, the C-reactive protein in CSF was positive in all cases (23, 100%) with bacterial meningitis. In non-meningitis cases, the C-reactive protein in CSF was negative in all cases (50, 100%). The results were similar to the study of Natani *et al.*, (2017), which found CSF-CRP positive in 35 cases of bacterial meningitis, 6 cases of aseptic meningitis, and negative in all cases of the control group. The C-reactive protein in CSF in cases of meningitis was positive in 23 cases, with a sensitivity of 100%, specificity of 70.4%, positive predictive value of 74.2%, and negative predictive value of 100%.

5. CONCLUSION

To conclude, the distribution of cases with aseptic meningitis was slightly higher than bacterial meningitis. Females were more predominant than males. The mean level of CRP, white blood cells (WBC), and protein in CSF were higher in bacterial than aseptic meningitis cases. Whereas, the mean concentration of sugar in CSF was higher in aseptic than control and the bacterial meningitis cases has the lowest surge concentration. The CRP in CSF was positive in all cases with bacterial meningitis and it was negative in all non-meningitis cases. Sensitivity was 100%, specificity was 70.4%, positive predictive value 74.2% and negative predictive value 100%. The CRP levels in CSF offers a high sensitivity and specificity. Therefore, the CSF- CRP can offers a valuable investigating method for differentiating bacterial from aseptic meningitis. It is a quick, sensitive and reliable diagnostic test.

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