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Original Research Article

Assessment of Cerebrospinal Fluid C - reactive protein in Bacterial Meningitis among Paediatric Age Group

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Abstract:

Background and Aim: Meningitis is a serious condition that can have severe consequences, including permanent brain damage, neurological issues, and even death. This study aimed to assess the diagnostic importance of CRP in CSF as an early indicator for distinguishing between bacterial and nonbacterial meningitis.

Material and Methods: An observational study was conducted in the paediatric ward of a tertiary care hospital in India over a period of 1 year. During the study period, a total of 100 children, ranging in age from 1 month to 12 years, were included in the study due to suspected meningitis. A lumbar puncture was conducted at the L3-L4 level, and a cerebrospinal fluid sample of no more than 3 ml was collected in 4 sterile containers. 1ml was sent to test for protein and sugar levels, while 0.5ml each was sent for CSF cytology and CSF-CRP. Additionally, 1ml was sent for CSF culture sensitivity and gram staining.

Results: The most common symptoms observed were fever (95%) and altered sensorium (92%), while the most frequently observed meningeal sign was neck rigidity (58%). Out of the 100 patients who were suspected of meningitis, the final diagnosis of bacterial meningitis was determined through CSF examination. It was found that 56% of these cases had a positive culture report. A significant majority of the patients who tested positive for the culture also had elevated levels of CRP in their cerebrospinal fluid. When analyzing cytology reports and CSF CRP positivity, it was discovered that 81.5% of the reports yielded positive results. When comparing abnormal CSF biochemical reports to CSF CRP positivity, it was discovered that 80% of cases were positive.

Conclusion: The levels of CRP in CSF demonstrate a moderate sensitivity and specificity, along with a high positive predictive value. It has been found that CSF CRP is a more effective marker in distinguishing bacterial meningitis.

Keywords: Altered Sensorium, CRP, CSF, Meningitis.

Introduction

Acute infections of the nervous system are a significant and frequently encountered issue in pediatrics. There are several different clinical syndromes that can occur, such as acute pyogenic meningitis, viral meningitis-encephalitis, focal infections like brain abscess and subdural empyema, and infectious thrombophlebitis. Recognizing and diagnosing a condition early, and promptly starting treatment, can be crucial for saving lives.

Meningitis is a major contributor to illness and death among children globally. Without proper treatment, the mortality rate can reach as high as 70 percent, and approximately 20 percent of individuals who survive bacterial meningitis may experience long-term consequences such as hearing loss and neurological impairment. [1,2] Meningitis remains a significant health concern in India, with a high rate of illness and death. Bacterial aetiological agents of pyogenic meningitis have been identified in various studies, including gram positive cocci and gram-negative bacilli. [3,4] Bacterial meningitis poses a serious threat to one's life. Recognizing the importance of early detection and administering the right antibiotics is essential in minimizing negative health outcomes and preventing loss of life.

Diagnosing bacterial meningitis can be quite challenging due to the complex clinical and biochemical presentation, which can be further complicated by previous inappropriate antibiotic use. It becomes even more challenging in

populations that are typically initially treated by private practitioners and receive a course of antibiotics before confirming the diagnosis. Patients are then directed to a tertiary care hospital as part of their treatment journey. When faced with this situation, it can be quite challenging to isolate the organisms from blood or CSF. [5]

Early diagnosis of bacterial meningitis from viral meningitis or meningoencephalitis is crucial for appropriate treatment. Antimicrobial therapy plays a significant role in improving neurological complications and survival rates. Preventing anti-microbial drug resistance and achieving positive outcomes. Diagnosing bacterial and viral meningitis can be challenging, particularly in children. Common laboratory tests may have low sensitivity and can be time-consuming. [6] Additionally, changes in glucose and protein levels, as well as cell count of cerebrospinal fluid, can be affected by inappropriate or inadequate antibiotic therapy. Latex agglutination is a fast and highly effective method for diagnosing meningitis, although it is not commonly accessible in developing countries. For diagnosing bacterial meningitis, the gold standard methods include measuring inflammatory markers, blood cell count, and blood culture. [7-9]

In addition, researchers have found that CSF cultures for pyogenic organisms are positive in only 30-60% of cases. [10] Given the absence of a definitive test for promptly and accurately diagnosing the cause of meningitis, it becomes crucial to identify a fast and dependable method for early bedside diagnosis. CSF-CRP is a test that fulfils all the necessary requirements. Unlike CSF cytology and biochemistry, it does not demand extensive expertise, skills, or specialized equipment to interpret the results. The purpose of this study was to assess the diagnostic value of CRP in CSF as an early indicator for distinguishing between bacterial and nonbacterial meningitis.

Material and Methods

This observational study was conducted in the paediatric ward of a tertiary care hospital in India over a period of 1 year. During the study period, a group of 100 children, ranging in age from 1 month to 12 years, were suspected of having meningitis based on various clinical criteria indicating central nervous system infection.

Inclusion Criteria

There are indications of meningeal irritation, such as neck rigidity, a positive Kernig sign, and a positive Brudzinski sign. Common symptoms of increased pressure within the skull include vomiting, headaches, cranial nerve problems, a bulging anterior fontanelle (soft spot on a baby's head), and Cushing's triad. Look out for signs of encephalopathy such as convulsions, lethargy, irritability, coma, altered sensorium, behavioral disturbances, and any other neurological deficit.

Excluded from the study were patients diagnosed with TB meningitis, children with a known immune function disorder, individuals with a known case of intracranial malformation, patients who were discharged against medical advice, those who were referred to a higher center, and individuals who failed to obtain a CSF sample even after three attempts.

Verbal consent was also obtained from the child if they were over 7 years old, in accordance with ICMR guidelines. As part of the patient assessment process, we collected socio-demographic data, conducted a thorough clinical history review, and performed a physical examination. Treatment was then started based on the initial diagnosis. A lumbar puncture was performed according to the established protocol, following the necessary informed consent. With utmost care for cleanliness, the patient was positioned in a knee-chest/flexion position, ensuring that the airway remained unobstructed. A lumbar puncture was performed at the L3-L4 level after the designated area was appropriately prepared and covered. A lumbar puncture needle of the appropriate size was used to perform the procedure. If LP was not successful at the L3-L4 level, they would attempt one level above and make a maximum of three attempts. If the patient was unable to provide CSF even after three attempts, they were excluded from the study. Ensure that the CSF sample does not exceed 3 ml and is collected in 4 sterile containers. Send 1 ml of the sample for protein and sugar analysis, and 0.5 ml each for CSF cytology and CSF CRP testing. Additionally, send 1 ml of the sample for CSF culture sensitivity and gram staining.

The measurement of C-reactive protein in the cerebrospinal fluid was conducted using the latex agglutination method. In this qualitative study, a CRP level above 6 mg/dl is considered positive. Confirmatory markers such as CSF culture and Gram stain, cytology, and biochemical analysis were utilized. The CSF- CRP was evaluated in comparison to these established parameters. The patients' final diagnosis was determined based on the working diagnosis mentioned below.

When it comes to diagnosing bacterial meningitis, one key factor to consider is the positivity of the CSF culture. This is especially important among cases where meningitis is suspected clinically, regardless of other parameters. According to various Indian studies, it has been found that cerebrospinal fluid culture for pyogenic organisms is positive in only 30-60% of cases. In cases where the culture results were negative, pyogenic meningitis was diagnosed if certain CSF

parameters were met. These parameters included a cellularity of leukocytes greater than 10 with a predominance of neutrophils greater than 20%, protein levels exceeding 40 mg/dl, and sugar levels below 40 mg/dl or less than 2/3rd of the parallel blood sugar. The cerebrospinal fluid shows signs of lymphocytic pleocytosis (5 to 500 cells/ml), slightly increased protein levels (30 to 65 mg/dl), and normal glucose levels. It's important to note that a normal CSF examination does not rule out the possibility of viral encephalitis.

A seizure can occur when a child between the ages of 1 month and 5 years experiences a high fever (above 38.3 degrees Celsius), without any signs of infection or electrolyte imbalance in the central nervous system. This type of seizure is known as a febrile seizure and is typically seen in children who have not had any previous seizures without fever. If it is focal and prolonged, it is considered complex.

Acute encephalopathy is frequently observed as a neurological disorder linked to dengue virus infection. There are various factors that can contribute to the development of dengue encephalopathy, leading to a decreased level of consciousness. These factors include prolonged shock, lack of oxygen, swelling in the brain, metabolic imbalances, bleeding in the body or brain, acute liver failure, or kidney failure. CSF analyses typically show normal levels of protein, glucose, and cell count.

Acute encephalopathy there is a condition that affects the brain's function, causing cognitive disorders, convulsions, and mood/personality disorders. It typically starts suddenly and does not show any abnormalities in the cerebrospinal fluid. Radiological evidence indicates encephalopathy, although the findings are not specific. There are different possible causes for this condition, including autoimmune, idiopathic, or metabolic factors.

Statistical Analysis

The recorded data was organized and inputted into a spreadsheet computer program (Microsoft Excel 2019) before being transferred to the data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were reported using measures such as means and standard deviations or median and interquartile range, depending on their distribution. The data for qualitative variables were displayed as counts and percentages. Confidence level and level of significance were set at 95% and 5% respectively for all tests.

Results

There were 100 patients diagnosed with bacterial meningitis. A significant proportion of children (46%) fell within the age range of 1 month to 1 year, with an average age of 27.80±1.40 months among the patients. The age range of the patients varied from 1 month to 12 years. According to Table 1, there was a male to female ratio of 1.1:1.

The most common symptoms observed were fever (95%) and changes in mental state (92%), while the most frequently observed sign of meningeal inflammation was neck rigidity (58%).

In 5 cases, developmental milestones were delayed, with 4 of them having a history of NICU stay in their earlier life. According to the national immunization schedule, only 12% of children received the recommended immunizations, while 9% did not receive any vaccines at all. During the neurologic assessment, there were indications of an altered mental state in 34% of cases, abnormal findings in cranial nerve examinations in 10% of cases, and abnormal motor function in 14% of cases.

Out of the 100 patients who were suspected of meningitis, the final diagnosis of bacterial meningitis was determined through CSF examination. It was found that 56% of these cases had a positive culture report. For individuals with negative reports (44 cases), diagnosis was determined using CSF protein, CSF sugar, and CSF microscopy reports. In three cases where routine microscopy was performed on culture negative samples, the results were normal. It is worth noting that all three patients had received antibiotics prior to the examination of their cerebrospinal fluid. According to the study findings, the average protein levels in children were 74 mg%, while the average CSF sugar in the study group was 58 mg%.

Pneumococcus was the most frequently isolated organism in CSF culture, accounting for 53% of the cases. Based on the findings, it was observed that ceftriaxone showed the highest sensitivity in the CSF, followed by cefotaxime and amikacin. It was noted that the CRP in CSF was positive in the majority of children diagnosed with bacterial meningitis, specifically 84, while it was negative in 16 children. Among the children who were diagnosed with conditions other than meningitis, 3 cases showed a positive CRP result while 15 cases showed a negative result. In children with meningitis, the average CRP level was 15.50±0.58 mg/l.

The majority of patients with positive cultures also had elevated levels of CRP in their cerebrospinal fluid. When examining cytology reports alongside CSF CRP positivity, it was discovered that 81.5% of the reports yielded positive results. When comparing abnormal CSF biochemical reports with CSF CRP positivity, it was discovered that 80% of them tested positive. Out of 100 cases of bacterial meningitis, 82 children tested positive for CSF CRP while the CSF culture came back negative for

18 children who tested negative for CSF CRP. Among the 88 children who tested positive for CSF CRP, 85 of them with meningitis had some organism detected in their CSF culture. On the other hand, the CSF culture was negative for 46 children without meningitis.

Table 1: Distribution of patients according to age and gender

Age (years)	Number of patients		Total
	Male	Female	
1 month to 1 year	33	13	46
>1 to 3	9	8	17
>3 to 6	7	14	21
>3 to 6	3	13	16
Total	52	48	100

Table 2: Clinical features of patients

Clinical features	Number	Percentage
Fever	95	95
Altered sensorium	92	92
Convulsions	88	88
Vomiting	34	34
Headache	23	23
Irritability	21	21
Meningeal signs		
Neck rigidity	58	58
Kernig sign	39	39
Brudzinski sign	33	33
Tachycardia	60	60
Febrile on admission	32	32
Shock	18	18
Cushing's triad	13	13
Hepatomegaly	4	4
Splenomegaly	3	3

Discussion

CRP is an acute phase protein produced by hepatocytes in response to infection or inflammation. The median concentration of serum C-reactive protein in a healthy individual is typically 0.8mg/l. The concentration of CRP in the cerebrospinal fluid (CSF) is significantly lower compared to that in the serum. Stimulation of C-reactive protein production is observed in cases of meningeal irritation. Production of this substance is regulated by Interleukin-6 and it has the ability to attach to polysaccharides found in various bacteria, fungi, and protozoal parasites. CRP can be found in serum or fluids closely linked to affected tissues in most inflammatory diseases. [13-15]

Characteristic features of bacterial meningitis include polymorphonuclear leukocytosis, low glucose concentration, and increased protein concentration in the cerebrospinal fluid (CSF). [16] In certain cases, bacterial meningitis can have unusual CSF manifestations, making it difficult to use white blood cell count, total protein, and glucose levels as reliable markers for differential diagnosis. This is mainly because of their low sensitivity. Glucose concentrations in the CSF of patients with viral meningitis can sometimes be similar to those seen in bacterial meningitis. However, CRP, a non-specific indicator, proved to be a highly reliable method for determining the type of infection. CSF-CRP should not be considered a substitute for the thorough examination of CSF biochemistry, cytology, and culture. It can be used to confirm a diagnosis, particularly when there are limitations on other diagnostic tests. [17]

Fever was a frequently reported symptom among patients with bacterial meningitis, often accompanied by changes in mental alertness. Neck rigidity was the most frequently observed meningeal sign. Other authors have also made a similar observation. [18,19] According to the neurologic assessment, it was found that the mental status of 34% of children was abnormal. Out of the 100 patients, 13 needed assistance with breathing upon admission due to a GCS score below 8/15. Ten patients exhibited cranial nerve involvement, with the majority experiencing lateral rectus palsy (VIth nerve). Thirteen patients exhibited abnormality in tone and power.

Out of the 100 cases of bacterial meningitis, 56 were found to have a positive culture report. In three cases where routine microscopy was performed on culture negative samples, the results were normal. It is worth noting that all three

patients had received antibiotics prior to the examination of their cerebrospinal fluid. CRP production increases as a quick and reliable response to many types of microbial infections. Its measurement has proven to be valuable in diagnosing and managing various infectious conditions. [20,21] The most frequently found organism in CSF culture was pneumococcus (Streptococcus pneumoniae). It appears that the low immunization coverage of the pneumococcal vaccine among economically disadvantaged families being served by the center is a contributing factor. Other studies conducted in different locations have also made similar observations, with streptococcus pneumonia being the most common isolates. [22,23]

It was noted that the presence of CRP in the cerebrospinal fluid was detected in the majority of children diagnosed with bacterial meningitis, specifically 83 cases. However, it was not detected in 17 children. Among the children diagnosed with conditions other than meningitis, 3 cases showed a positive CRP result, while 15 cases had a negative result. These findings align with previous studies conducted by Bansal et al [17], Hansson et al [24], and Komorowski et al [25], which reported that CSFCRP was an effective indicator for rapidly diagnosing meningitis in 60% of adults. According to a study conducted by Gray et al., it was found that CRP levels exceeding 100 ng/ml were observed in 95% of cases of bacterial meningitis. [26] According to a study by Singh et al., the CRP level was found to be positive in 84% of cases of bacterial meningitis, while it was negative in all cases of aseptic meningitis. No correlation was found between the level of CSF-CRP and the total and differential cell count in the cerebrospinal fluid of septic cases. [27]

Among the 100 children, 57 tested positive for CSF culture. Out of those, 52 also tested positive for CSF-CRP, while 5 cases were negative for CSF-CRP. CSF-CRP is considered a highly dependable and early indicator for distinguishing between bacterial and non-bacterial meningitis. [28] Estimating CRP levels can be a more effective method for diagnosing cases of acute bacterial meningitis compared to relying solely on culture. It can also be helpful in tracking the progress of meningitis. [27] The concentration of CRP in cerebrospinal fluid (CSF) can vary and is typically lower than in plasma.

The amount of CRP released into CSF from plasma by ultrafiltration and secretion by inflamed meninges determines the outcome. Based on the available evidence, it seems that CSF leakage or passive diffusion from the blood is a more likely explanation than active secretion. CSFCRP showed a strong correlation with other CSF parameters. CSF culture is currently considered the gold standard for diagnosing meningitis.

However, there are some downsides to consider, including a low positivity rate and the potential for contamination. Administering antibiotics, delayed analysis, and partially treated meningitis can also affect the CSF picture. CSF-CRP can be a useful test in certain situations, as its levels remain stable when analyzed early in the course of illness. The study had some limitations, including a small sample size and the absence of quantitative estimation of CSF-CRP. Having a larger sample size and quantitatively estimating CSF-CRP would have provided a more comprehensive understanding. This study aims to assess the diagnostic significance of CSF-CRP and its role in distinguishing between bacterial and non-bacterial meningitis.

Conclusion

CRP levels in CSF have been found to provide a moderate level of sensitivity and specificity, along with a high positive predictive value. It appears that CSF CRP is a more effective marker for distinguishing bacterial meningitis. In addition, the CSF-CRP can serve as a diagnostic marker to distinguish between purulent and non-purulent meningitis. CSF-CRP is a valuable tool for diagnosing bacterial meningitis, providing a simple, rapid, and accurate alternative to traditional methods like biochemistry, cultures, and smears. It can serve as an initial test for diagnosing bacterial meningitis while waiting for other confirmatory test results.

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