

Cerebrospinal fluid (CSF) analysis: An important tool to differentiate between Bacterial Meningitis and Viral Meningitis

ABSTRACT

Objective: To analyze cerebrospinal fluid (CSF) in acute bacterial and viral meningitis patients and differentiating between bacterial and viral meningitis upon the changes observed in CSF compositions.

Methodology: This was a hospital based study conducted from June 2016 to November 2017 in the infectious disease unit of Chattagram Maa-O-Shishu general hospital, Chittagong. The admitted patients who fulfilled the criteria were included in the study. The CSF analysis was done on the first spinal tap and it contained protein level, lactate level, glucose, cell count, Gram's stain and culture. Blood count, blood glucose, blood culture were also investigated for all the patients.

Results: A total 93 patients were included in the study. Out of 35 bacterial meningitis patients, *S. pneumoniae*, *N. meningitidis* and *E. coli* were found in 51.43% whereas 48.57 were culture negative. Both CSF protein and lactate values were found higher in bacterial than in viral meningitis, with mean 298.33 ± 88.32 and 95.05 ± 49.42 mg/dl (p value <0.001) respectively and 8.35 ± 3.18 mmol/L and 3.4 ± 5.62 mmol/L (p value <0.001) respectively. Higher leukocyte count was also found in bacterial than in viral meningitis, 22.82 ± 6.71 and 10.43 ± 4.31 cell/culture (p value <0.001) respectively. However, lower CSF glucose level

23 was found in bacterial than in viral patients, with mean 175.67 ± 49.87 and 132.26 ± 38.72
24 mg/dl (p value <0.001) respectively.

25 **Conclusion:** CSF analysis (CSF protein, lactate, glucose values) as well as blood glucose and
26 leukocyte count may provide a reliable, rapid way to differentiate between acute bacterial
27 from viral meningitis which may come into the aid in disease management.

28 **KEY WORDS:** *Meningitis, Bacterial, Viral, CSF analysis, Protein status, Lactate level.*

29 INTRODUCTION

30 Meninges are the protective membranes that cover the brain and spinal cord and meningitis is
31 the acute inflammation of the meninges (1). About 8.7 million people suffered from
32 meningitis in 2015 which resulted in almost 379,000 deaths (2, 3). But the death toll due to
33 bacterial meningitis reduces to less than 15% when there is appropriate treatment (4). If not
34 treated quickly, Meningitis can lead to serious long-term consequences such
35 as deafness, epilepsy, hydrocephalus or cognitive deficits (5). Nuchal rigidity, sudden high
36 fever, and altered mental status are the classic triad of diagnostic signs of meningitis besides
37 photophobia, phonophobia, Kernig's sign or Brudzinski sign (6, 7). The distinction of viral
38 meningitis from bacterial meningitis is often very difficult as there is no gold standard
39 laboratory test and the clinical features are not specific, especially in young children (8, 9).
40 Cerebrospinal fluid analysis through lumbar puncture is the most used test in identifying or
41 ruling out meningitis besides blood tests, CT or MRI and Polymerase chain reaction (1, 10).
42 The presence and types of red blood cells, white blood cells, protein content
43 and glucose level are checked in a CSF sample as their values indicate the type of the
44 meningitis (11-13). As meningitis is life-threatening and has a high mortality rate, treatment
45 should not be delayed with wide-spectrum antibiotics like cefalosporin, vancomycin and
46 ampicillin while confirmatory tests are being performed (5, 14). However, to avoid resistance

47 and for effective treatment, it is very important to identify the type of meningitis promptly.
48 This study was undertaken to evaluate the cerebrospinal fluid changes in acute bacterial and
49 viral meningitis and the role of CSF differentials like the protein level, lactate level, CSF
50 glucose level, leukocyte count and blood glucose level in discriminating bacterial and viral
51 meningitis.

52 MATERIALS AND METHODS

53 The study was performed in the Department of Paediatrics and Pathology and Microbiology
54 and Biochemistry laboratory of Chattagram Maa-O-Shishu General Hospital, Agrabad,
55 Chittagong, during the period of June 2016 to November 2017. Total 93 subjects presenting
56 with the complaints of fever and features suggestive of meningitis were included in this study
57 without any specific predilection for race, religion and socioeconomic status. In all cases, the
58 suspected meningitis subjects were between 0 and 12 years old. The diagnosis of meningitis
59 was based on clinical findings and CSF gram staining, culture and chemical analysis.
60 Meningitis was defined as proven to be bacterial by a positive result on gram staining and/or
61 bacterial culture. Meningitis was probably bacterial if CSF was cloudy, the leukocyte count
62 in CSF was $>1500/\text{mm}^3$ with granulocytes representing $>50\%$, the ratio of glucose in CSF to
63 glucose in blood was <0.4 and the level of CSF protein $>200\text{mg/dl}$ (15). The CSF analysis
64 was performed on the first spinal tap and it included protein, lactate, glucose, cell count,
65 Gram's stain and culture. The quantity of protein in cerebrospinal fluid was evaluated by
66 automated clinical chemistry analyzers (Humalyzer 2000, Germany, Ultrasensitive protein)
67 (16). The CSF lactate level was estimated by Enzymatic Colorimetric method. Other
68 laboratory investigations including full blood count (FBC), blood sugar, blood culture were
69 also conducted for all the patients. The patients were treated according to the current
70 guidelines for the management of acute bacterial and viral meningitis.

71 **Inclusion criteria:**

72 1. Patient with clinical diagnosis of meningitis and CSF Gram's staining and/or culture
73 positive for bacteria.

74 2. Patient with clinical and CSF findings indicative of meningitis with negative CSF Gram's
75 staining and culture but positive blood culture for bacteria.

76 3. Clinically suspected and CSF changes suggestive of bacterial meningitis but CSF Gram's
77 staining, culture and blood culture negative and these patients were treated for bacterial
78 meningitis (Culture –ve bacterial meningitis).

79 4. Patients with clinical diagnosis of viral meningitis. The diagnosis of viral meningitis was
80 established by usual clinical and laboratory criteria, including appropriate history and
81 physical examination, CSF pleocytosis, negative bacterial culture and Gram's stain and CSF
82 protein and glucose concentration. (17)

83 **Exclusion criteria:**

84 1. Patients who received antibiotics before presenting to the hospital.

85 2. Patients with Tuberculosis and fungal meningitis.

86 3. Patients with concomitant illness such as HIV/on immunosuppressive therapy.

87 4. Conditions which can contribute in elevation of CSF lactate such as recent stroke, brain
88 hypoxia/ anoxia, brain trauma and seizures.

89 **Ethical consideration**

90 Informed parental consent was taken before enrolling the children into the study. The
91 procedure was fully explained to the parents & they were informed that if they wish they will

92 be able to withdraw them from the study & it would not in any way hamper the treatment.
93 Permission was also taken from the Hospital authority, Departmental head of the paediatric
94 unit and in charge of Biochemistry, Microbiology & Pathology lab in order to undertake the
95 study.

96 **Development of questionnaire**

97 A questionnaire was developed to obtain relevant information of demographic & socio-
98 economic data. The questionnaire also included anthropometric data, Birth history,
99 immunization history, past medical history & clinical information. The questionnaire were
100 coded & pre-tested before finalization. The questionnaire was both closed & open ended.

101 **Data analysis**

102 Collected data was checked for its completeness, correctness. Editing was done by employing
103 Statistical Package for Social Science (SPSS version 16.0) software package. A p-value of
104 <0.05 was considered indicative of a statistically significant difference.

105 **RESULTS**

106 A total 93 patients fulfilled the inclusion criteria, of whom 39 were male and 54 were female.
107 Among them, 48 had viral meningitis, 35 subjects had bacterial meningitis and 10 had
108 tubercular meningitis. Fever, headache, neck stiffness, nausea, vomiting were the most seen
109 signs and symptoms. Clinical signs and symptoms as reported by the paediatrician are
110 summarized in table 1. Out of 35 bacterial meningitis patients, *Streptococcus pneumoniae*
111 was isolated from 11 patients (31.43%), *Neisseria meningitidis* from 5 patients (14.29%) and
112 *Escherichia coli* from 2 patients (5.71%) while no microbial pathogens were detected in the
113 rest 17 patients (48.57%) (culture -ve bacterial meningitis). But their change in CSF was
114 indicative to bacterial meningitis. The CSF protein level was high in bacterial than viral

meningitis patients, with mean 298.33 ± 88.32 and 95.05 ± 49.42 mg/dl (p value <0.001) respectively (Figure 1). The CSF analysis also showed higher values of lactate level in bacterial meningitis with comparison to viral meningitis, 8.35 ± 3.18 mmol/L and 3.4 ± 5.62 mmol/L (p value <0.001) respectively. However, the CSF glucose level was found to be lower in bacterial meningitis than in viral meningitis, 9.63 ± 0.57 mg/dl and 57.96 ± 14.11 mg/dl (p value <0.001) respectively (Figure 2). High peripheral leukocyte count was found in bacterial meningitis than viral meningitis, 22.82 ± 6.71 and 10.43 ± 4.31 cell/culture (p value <0.001) respectively. 86% patient of bacterial meningitis showed leukocytosis, whereas only 18% of viral meningitis patient exerted slight increased white cell count. The blood glucose level was high in bacterial meningitis than in viral meningitis, 175.67 ± 49.87 and 132.26 ± 38.72 mg/dl (p value <0.001) respectively.

DISCUSSION

Discriminating between bacterial and viral meningitis is often very difficult as there are no specific signs and symptoms regarding this. Most of the seen common signs and symptoms are Bulged Fontanelles (85%), Neck rigidity (30%), Brudzinski sign (24%) and Kernig's sign (22%) (18). Cerebrospinal fluid (CSF) analysis is important in the differential diagnosis of patients with bacterial and viral meningitis (19). CSF protein and lactate values, C-reactive protein, serum procalcitonin and CSF/serum glucose ratio tests have been found useful in the detection of types of meningitis. However, CSF analysis, Gram's staining and culture still remains the most useful method in the distinction between bacterial and viral meningitis (11, 20). CSF samples are collected by lumbar puncture for further evaluation that may help in the differentiation of viral meningitis from bacterial. Gram staining does not always help as only about 60% of bacterial meningitis supports that and the percentage reduces to more 20% in cases where antibiotics are taken before sample was taken. Gram staining is also less reliable

in particular infections such as listeriosis. Microbiological culture is more sensitive as it identifies the organism in 70–85% of cases but it is time consuming (10, 13). The CSF Gram stain is positive in *Streptococcus pneumoniae* (90%), in *Haemophilus influenzae* (86%), in *Neisseria meningitidis* (75%), in gram negative bacilli (59%) and 33% in *Listeria monocytogenes* (21). The CSF protein level was found to be high in bacterial meningitis than in viral meningitis in many cases which supports our current finding. One of many studies showed higher CSF protein level in bacterial meningitis than viral meningitis, with mean 641.01 ± 428.52 vs. 91.74 ± 44.68 mg/dl (9, 11). In *Streptococcus*-mediated meningitis, the protein level was found 243 mg/dl while that in culture negative bacterial meningitis and in viral meningitis were found 223 mg/dl and 112.12 mg/dl respectively (11, 18). Increased CSF lactate level indicates bacterial meningitis as does a higher white blood cell count (10). The clinical relevance of lactate levels in CSF has been shown by some authors (22, 23). Lactate level less than 35 mg/dl in a person who has not previously taken any antibiotics is not likely to be a victim of bacterial meningitis. However, lactate also increases in viral meningitis patients, the maximum value encountered in our study group being 3.3 mmol/L (8). In bacterial meningitis, the CSF glucose level is usually decreased (<40 percent of simultaneously measured serum glucose) but in viral meningitis CSF glucose is normal or slightly decreased (19). However, lower CSF glucose level was found in bacterial meningitis in comparison to viral meningitis, mean 26.50 ± 21.56 and 67.00 ± 18.96 mg/dl, with statistically significant difference (p value <.001) (1). The white blood cell, usually neutrophil-predominant indicates bacterial meningitis whereas usually lymphocyte-predominant white blood cell indicates viral meningitis, although it is not reliable indicators at the beginning (13, 24). The CSF leukocyte count was higher with predominant polymorphs (95%) in bacterial than viral (7%) cases, with mean cell count 4522.25 ± 2809.65 and 206.31 ± 218.9 3cell/mm³ (18). However, there are cases where lower CSF leukocyte count was

found in proven acute bacterial meningitis (9). The blood glucose and peripheral leukocyte count was also high in bacterial than viral meningitis, 179.49 ± 55.10 and 135.21 ± 39.31 mg/dl and 20.76 ± 8.02 and 8.90 ± 2.25 cell/cul respectively that support our current findings (18).

CONCLUSION

In distinguishing acute bacterial meningitis from viral meningitis, the CSF analysis is an important tool that plays a significant role. The CSF protein and lactate values as well as CSF glucose value can rapidly differentiate between bacterial and viral meningitis when conventional Gram's staining and culture are negative. The CSF analysis provides rapid and reliable diagnostic information with higher sensitivity and positive predictive value that helps in differentiating bacterial from viral meningitis which may facilitate the disease management more precisely avoiding unnecessary administration of antibiotics.

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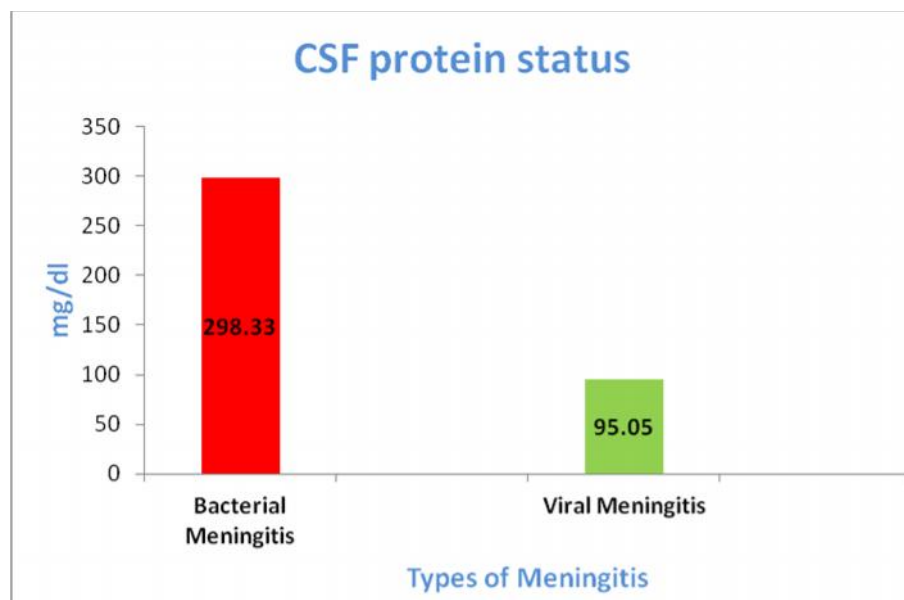
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Table and Figures

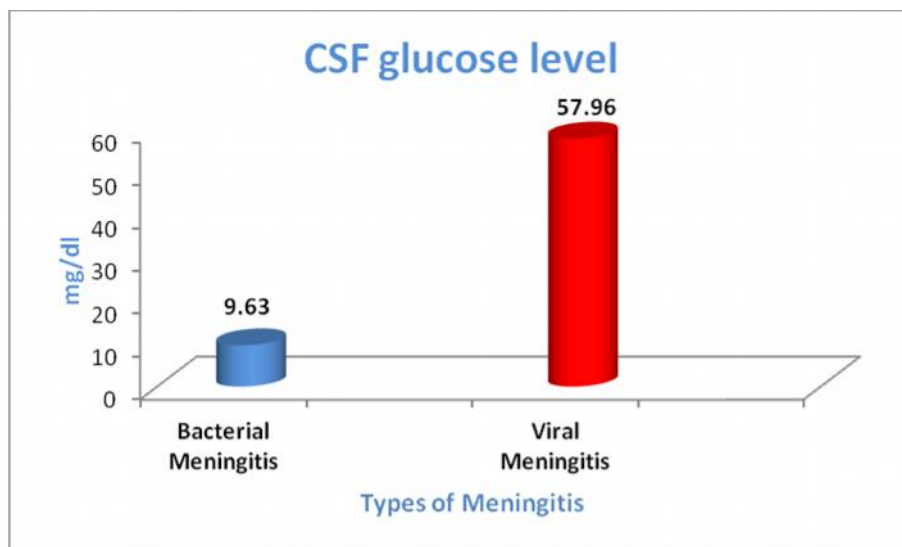
238 Table 1: Clinical signs and symptoms as reported by the paediatrician

Signs	and	Viral Meningitis	Bacterial Meningitis	Tubercular Meningitis

Symptoms			
Fever	39/48 (81%)	32/35 (91%)	8/10 (80%)
Headache	36/48 (75%)	9/35 (26%)	4/10 (40%)
Neck Stiffness	41/48 (85%)	25/35 (71%)	7/10 (70%)
Kernig's Sign	12/48 (26%)	8/35 (25%)	3/10 (30%)
Brudzinski's Sign	11/48 (24%)	7/35 (22%)	2/10 (20%)
Bulged Frontalis	17/48 (36%)	10/35 (31%)	3/10 (30%)
Nausea	37/48 (76%)	21/35 (61%)	5/10 (50%)
Vomiting	32/48 (68%)	16/35 (46%)	4/10 (40%)
Convulsions	2/48 (4%)	7/35 (22%)	1/10 (10%)



239 Figure 1: Mean CSF protein level in acute bacterial and viral meningitis



240 Figure 2: Mean CSF glucose level in acute bacterial and viral meningitis