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Assessment of Cerebrospinal Fluid (CSF) to Differentiate between Bacterial Meningitis and Viral Meningitis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SA, AR and MUQ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AKA, FN and RHC managed the analysis of the study. Author CMMH managed the literature searches. All authors read and approved the final manuscript.

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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.

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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 was found in bacterial than in viral patients, with mean 175.67 ± 49.87 and 132.26 ± 38.72 mg/dl (p value <0.001) respectively.
Conclusion: CSF analysis (CSF protein, lactate, glucose values), as well as blood glucose and leukocyte count, may provide a reliable, rapid way to differentiate between acute bacterial from viral meningitis which may come into the aid in disease management.

Keywords: Meningitis; bacterial; viral; CSF analysis; protein status; lactate level.

1. INTRODUCTION

Meninges are the protective membranes that cover the brain and spinal cord and meningitis is the acute inflammation of the meninges [1]. About 8.7 million people suffered from meningitis in 2015 which resulted in almost 379,000 deaths [2,3]. However, the death toll due to bacterial meningitis reduces to <15% when there is appropriate treatment [4]. If not treated quickly, meningitis can lead to serious long-term consequences such as deafness, epilepsy, hydrocephalus or cognitive deficits [5]. Nuchal rigidity, sudden high fever, and altered mental status are the classic triad of diagnostic signs of meningitis besides photophobia, phonophobia, Kernig's sign or Brudziński sign [6,7]. The distinction between viral meningitis and bacterial meningitis is often very difficult as there is no gold standard laboratory test. In addition, the clinical features are not specific, especially in young children [8,9]. Cerebrospinal fluid analysis through lumbar puncture is the most used test in identifying or ruling out meningitis besides blood tests, computed tomography (CT) scan or magnetic resonance imaging (MRI) and polymerase chain reaction (PCR) [1,10]. The presence and types of red blood cells, white blood cells, protein content and glucose level are checked in a CSF sample as their values could indicate the type of the meningitis [11-14]. As meningitis is a life-threatening disease and has a high mortality rate, treatment should not be delayed. However, to avoid resistance and for effective treatment, it is very important to identify the type of meningitis promptly. This study was undertaken to evaluate the cerebrospinal fluid changes in suspected bacterial and viral meningitis cases and the role of CSF differentials such as the protein level, lactate level, CSF glucose level, leukocyte count and blood glucose level in differentiating between bacterial and viral meningitis.

2. MATERIALS AND METHODS

The study was performed in the Department of Paediatrics and Pathology and Microbiology and Biochemistry laboratory of Chattagram Maa-O-Shishu General Hospital, Agrabad, Chittagong, during the period of June 2016 to November 2017. Total 93 subjects presenting with the complaints of fever and features suggestive of meningitis were included in this study without any specific predilection for race, religion and socioeconomic status. In all cases, the suspected meningitis subjects were between 0 and 12 years old. The diagnosis of meningitis was based on clinical findings and CSF gram staining, culture and chemical analysis. Meningitis was defined as proven to be bacterial by a positive result on gram staining and/or bacterial culture. Meningitis was probably bacterial if CSF was cloudy, the leukocyte count in CSF was >1500/mm^3 with granulocytes representing >50%, the ratio of glucose in CSF to glucose in blood was <0.4 and the level of CSF protein >200 mg/dl [15]. The CSF analysis was performed on the first spinal tap and it included protein, lactate, glucose, cell count, Gram's stain and culture. The quantity of protein in cerebrospinal fluid was evaluated by automated clinical chemistry analyzers (Humalyzer 2000, Germany, Ultrasensitive

protein) [16]. The CSF lactate level was estimated by Enzymatic Colorimetric method. Other laboratory investigations including full blood count (FBC), blood sugar, blood culture were also conducted for all the patients. The patients were treated according to the current guidelines for the management of acute bacterial and viral meningitis.

2.1 Inclusion Criteria

1. Patient with clinical diagnosis of meningitis and CSF Gram's staining and/or culture positive for bacteria.
2. Patient with clinical and CSF findings indicative of meningitis with negative CSF Gram's staining and culture but positive blood culture for bacteria.
3. Clinically suspected and CSF changes suggestive of bacterial meningitis but CSF Gram's staining, culture and blood culture negative and these patients were treated for bacterial meningitis (Culture –ve bacterial meningitis).
4. Patients with clinical diagnosis of viral meningitis. The diagnosis of viral meningitis was established by usual clinical and laboratory criteria, including appropriate history and physical examination, CSF pleocytosis, negative bacterial culture and Gram's stain and CSF protein and glucose concentration [17].

2.2 Exclusion Criteria

1. Patients who received antibiotics before presenting to the hospital.
2. Patients with Tuberculosis and fungal meningitis.
3. Patients with a concomitant illness such as HIV/on immunosuppressive therapy.
4. Conditions which can contribute in elevation of CSF lactate such as recent stroke, brain hypoxia/ anoxia, brain trauma and seizures.

2.3 Ethical Consideration

Informed parental consent was taken before enrolling the children into the study. The procedure was fully explained to the parents & they were informed that_if they wish they will be able to withdraw them form the study & it would not in way hamper the treatment. Permission was also taken from the Hospital authority, Departmental head of the paediatric unit and in charge of Biochemistry, Microbiology & Pathology lab in order to undertake the study.

2.4 Development of Questionnaire

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

2.5 Data Analysis

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

3. RESULTS

A total 93 patients, of whom 39 were male and 54 were female. Among them, 48 had viral meningitis, 35 subjects had bacterial meningitis and 10 had tubercular meningitis (excluded due to exclusion criteria). Fever, headache, neck stiffness, nausea, vomiting were the most seen signs and symptoms. Clinical signs and symptoms as reported by the paediatrician are summarized in Table 1. Out of 35 bacterial meningitis patients, *Streptococcus pneumoniae* was isolated from 11 patients (31.43%), *Neisseria meningitidis* from 5 patients (14.29%) and *Escherichia coli* from 2 patients (5.71%) while no microbial pathogens were detected in the rest 17 patients (48.57%) (culture -ve bacterial meningitis). But their change in CSF was indicative of 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 <.001) respectively (Fig. 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 (Fig. 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.

Table 1. Clinical signs and symptoms as reported by the paediatrician

Signs and symptoms	Viral meningitis	Bacterial meningitis	Tubercular meningitis
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%)

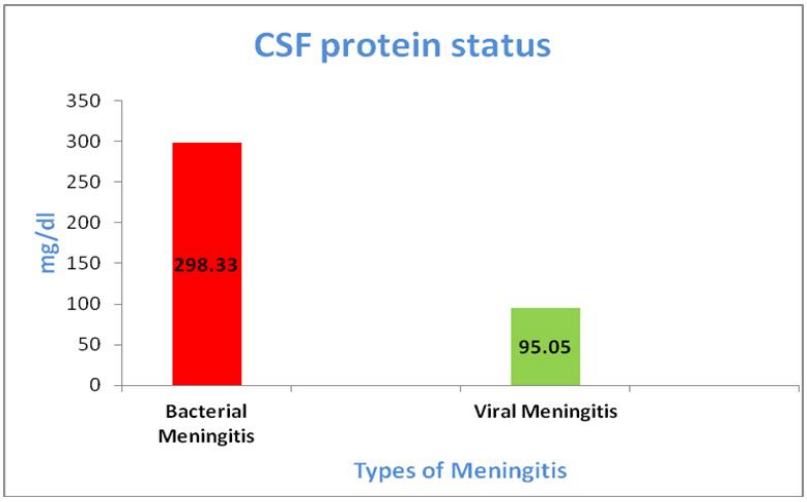

Fig. 1. Mean CSF protein level in acute bacterial and viral meningitis

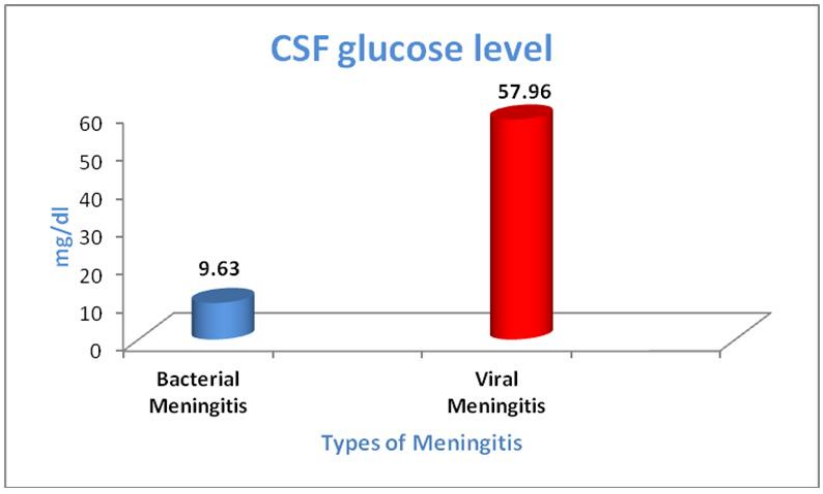

Fig. 2. Mean CSF glucose level in acute bacterial and viral meningitis

4. 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 Fontanels (85%), Neck rigidity (30%), Brudziniski 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 remain the most useful method in the distinction between bacterial and viral meningitis [11,20]. CSF samples are collected by lumber 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 the 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 support 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 a 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 3 cell/mm^3 [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 were 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].

5. 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.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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