Role of Cerebrospinal Fluid Lactate in Diagnosing Meningitis in Critically Ill Patients

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Role of Cerebrospinal Fluid Lactate in Diagnosing Meningitis in Critically Ill Patients

INTRODUCTION

Meningitis is a life-threatening condition associated with high mortality and morbidity and may affect any patient's age group [1]. Patients with meningitis may present with headache, photophobia, and neck stiffness and may develop confusion and coma in the later stages [2]. Older patients are more prone to have altered mental status and focal neurologic deficits rather than neck stiffness and headache[3,4]. However, these are non-specific; hence, a high index of suspicion is required to make the correct diagnosis. As early diagnosis and specific treatment may improve outcomes, every attempt must be made to make an early etiological diagnosis to institute specific therapy [5].

The most common form of meningitis is aseptic meningitis. These cases are primarily viral, and enterovirus is the most common etiological organism reported in immune-competent individuals[6,7]. Aseptic and bacterial meningitis are similar in clinical presentation, but patients with bacterial meningitis appear more ill clinically. All patients with symptoms suggestive of meningitis should undergo lumbar puncture (LP) at the earliest and cerebrospinal fluid (CSF) assessment for definitive diagnosis and appropriate treatment. On cytological and biochemical analysis of CSF, lymphocytic
1 pleocytosis with normal glucose level and a normal to slightly elevated protein level are seen in aseptic meningitis. Whereas bacterial meningitis

characteristically has a very elevated and predominantly neutrophilic pleocytosis with low glucose level, decreased CSF/serum glucose ratio (<0.4), and a high protein level. The reported sensitivity and specificity of CSF total leucocyte count (TLC), proteins, and sugars for diagnosing meningitis are 80%, 89%; 97%, 85%; 93%, and 49%, respectively[8].

CSF Gram and acid-fast bacilli (AFB) stains are quick methods of detecting the organism, but they lack sensitivity (50 to 80%). CSF cultures, which are positive in, at best, 80% of cases of bacterial meningitis, have a long turn-around time of 48 hours and may be falsely negative in patients already on antibiotics. The sensitivity of CSF Gram stain and cultures is less than 50% in such patients[9]. A real-time polymerase chain reaction (rt-PCR) based meningoencephalitis panel is useful for the etiological diagnosis of meningitis. Even though it has good sensitivity and specificity, its application is restricted due to its limited availability and high cost. Hence, there is a need for a readily available test that is easy to apply and can diagnose meningitis and differentiate between bacterial and non-bacterial causes of meningitis.

Blood lactate is tested in almost all critically ill patients in intensive care units (ICUs) and has been used to guide treatment and predict prognosis. In contrast, CSF lactate is rarely tested. Normal CSF lactate levels are 1.2-2.1 mmol/l, but they may range from 0.6-3.1 mmol/l[10]. Anaerobic glycolysis of brain tissue due to decreased cerebral blood flow and oxygen uptake may increase lactate concentration in CSF patients with meningitis[11]. Hence, CSF lactate has been suggested as an excellent marker to diagnose meningitis and may be a better marker than CSF TLC, sugar, and proteins[12,13]. In addition, it is inexpensive, has high test-retest reliability and is also readily available even in the resourcepoor world, where neurological imaging may be difficult to obtain. However, most of the studies have been done on post-neurosurgical and brain trauma patients, and there is a dearth of data regarding its accuracy in critically ill medical patients with suspected meningitis.

MATERIAL AND METHODS

A prospective, observational cohort study was carried out in a neuro-medical ICU of a tertiary care hospital in India from December 2019 to October 2021. Institutional Human Ethics Committee approval was obtained before the commencement of the study (Reference number: ....). After explaining the study protocol, written informed consent was obtained from all the participants. Those patients fulfilling inclusion criteria, patients older than 18 years, admitted with suspected meningitis in ICU, were serially recruited. Patients who refused to consent to the study, those with a peripheral sensorineural deficit, and those with any contraindication to the LP procedure were excluded. Trained intensivists performed LP with full aseptic precautions per the clinical protocols, and samples were sent immediately to the hospital laboratory in sterile containers. CSF cytology, biochemical parameters, culture and PCR-based meningoencephalitis panel, were evaluated. CSF lactate levels were measured in all the patients. The final diagnosis of meningitis was made based on the clinical picture, CSF analysis, culture and PCR reports. The sensitivity, specificity, and positive and negative predictive value of CSF lactate, to diagnose meningitis were calculated. The efficacy of CSF lactates was compared with other commonly employed tests like CSF TLC, proteins, and sugar levels. Correlation of CSF lactate with CSF culture and PCR was also performed. CSF lactates were also compared in patients with bacterial versus non-bacterial causes of meningitis. Hospital and ICU length of stay (LOS), need for invasive mechanical ventilation (IMV), and ICU mortality were also recorded.

Statistical analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois). Normally distributed continuous variables were compared using the unpaired t-test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical
2 variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. The area under receiver operating characteristics (AUROC) analysis was calculated to determine optimal cut-off values for CSF TLC, protein, sugar, and lactate levels. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference.

RESULTS

Seventy-one patients who fulfilled the inclusion criteria were included in the final analysis and divided into two groups, meningitis and non-meningitis groups, based on the clinical diagnosis of meningitis. Their basic characteristics, clinical parameters and hospital course are given in table 1.

The mean values of CSF TLC, proteins and lactates were significantly higher in the meningitis group, whereas mean value sugar levels were significantly higher in non-meningitis groups (Table 2). There was a significant correlation of CSF lactate levels with CSF cultures, meningoencephalitis PCR-based panel, and a combination of both (CSF cultures and meningoencephalitis panel) with a p-value < 0.05.

As shown in Table 3, the CSF lactate cut-off point for the diagnosis of meningitis, obtained by analyzing the ROC curve, was >2.7 mmol/L with an AUC of 0.81 (95% CI 0.69 - 0.93). Sensitivity was 82.6%, specificity 72.9%, positive predictive value 59.4%, negative predictive value 89.7% and accuracy 76.1%.

The causes of meningitis and the final diagnosis of patients in the non-meningitis group are given in table 4. Out of 23 meningitis patients, 12 had bacterial meningitis, and 11 had non-bacterial meningitis. CSF lactate levels were significantly higher in bacterial meningitis (8.9 ± 4.7) than in non-bacterial meningitis (4.2 ± 3.8), p value=0.006.

DISCUSSION

Even though central nervous system (CNS) infections account for only 2.9% of infections in ICU, they are associated with high morbidity and mortality, ranging from 17-40%[14,15]. These patients' outcomes depend on the etiological organism and the kind of care provided[15]. Hence, making an early diagnosis and initiating specific treatment measures is imperative. In the present prospective cohort study, we found that CSF lactate had good accuracy, sensitivity and specificity in diagnosing meningitis and showed a good correlation with CSF cultures and RT-PCR-based panels. In addition, it may also aid in differentiating between bacterial and non-bacterial causes of infective meningitis.

In critically ill patients, there could be several differential diagnoses that may mimic meningitis symptoms. These include acute stroke, tumours, toxins, autoimmune and paraneoplastic diseases and cerebral or epidural abscesses.

In addition, several metabolic derangements like sepsis and electrolyte disturbances may also present similarly. In the present study, these factors were the most common causes of neurological derangement in the non-meningitis group. The typically described triad of headache, fever and neck rigidity is present in less than 50% of patients with meningitis; hence a high degree of suspicion is required[3].

CSF analysis remains the cornerstone for diagnosing meningitis and making the etiological diagnosis. The etiological organism causing meningitis depends on several patient conditions, including age, immunocompromised status, sinusitis or endocarditis, and any traumatic brain injury, neurosurgery or indwelling neurological devices or catheters. Streptococcus pneumoniae has been reported to be the commonest cause of bacterial meningitis, similar to the results of our study. Haemophilus influenza and Staphylococcus aureus are rare causes of meningitis in adult patients and are generally secondary to other underlying clinical conditions like sinusitis and endocarditis[16]. The reported incidence of Mycobacterium tuberculosis as a cause of acute meningitis is around 5%, but it may be higher in countries with a higher prevalence of tuberculosis[17]. Among the viral causes, the Varicella-zoster virus is most commonly implicated in immunocompromised patients and the Herpes simplex virus in immunocompetent adults[17].

Presently, there is a need for a definitive test to enable rapid and accurate diagnosis, and hence the search for an ideal test continues. Apart from the routinely employed tests, several other CSF markers have been tested for their efficacy in diagnosing meningitis. Tests like CSF adenosine deaminase (ADA) and cortisol have explicitly been evaluated for the diagnosis of tubercular

meningitis, and specific other markers like CSF TNF-alpha, IL-6, IL-8 and IL-17 levels have been tested for the diagnosis of nosocomial meningitis, with varied success[18-20].
CSF culture is still the gold standard for diagnosing bacterial meningitis, with a reported sensitivity of up to 80%. However, its efficacy in diagnosing other causes of infective meningitis is limited[21,22]. Its clinical application is also limited by a long turn-around of 48 hours, thus delaying the initiation of appropriate early treatment. Moreover, its efficacy is further hampered in patients who have already received antibiotics.

Newer tests like RT-PCR-based meningitis-encephalitis panel (FilmArray PCR),
3 a qualitative multiplex nucleic acid-based in-vitro diagnostic test, have been developed and are being increasingly used to diagnose meningitis[23]. This test has several advantages, including rapid turn-around time, good sensitivity and specificity (above 90%) and minimal effect of previous antibiotic exposure[24]. In addition, this test may help diagnose non-bacterial causes of meningitis, including viral and fungal meningitis and culture-negative cases[23]. This panel is capable of simultaneous identification of 14 different organisms, including multiple bacterial (Escherichia Coli, H. Influenzae, L. Monocytogenes, N. meningitides, Strepto. agalactiae, Strepto. pneumoniae), viral (Cytomegalovirus, Enterovirus, HSV 1; HSV 2; HHV 6, VZV) and fungal/yeast (Cryptococcus neoformans/gatti) nucleic acid directly from CSF specimen and may help diagnose complex cases too[25].

CSF lactate is now recognized as a valuable marker for diagnosing acute meningitis. It has shown to be a helpful marker in diagnosing nosocomial meningitis and has shown up to 100% sensitivity for diagnosing bacterial meningitis[19]. As it is a rapid, inexpensive and readily available tool, it may guide physicians in making an early diagnosis of acute meningitis and differentiating bacterial from other causes of meningitis. Nevertheless, it cannot be used as a standalone test but may be helpful to our routine CSF analysis. The value of CSF lactates does not depend on the serum lactate levels as ionized lactate crosses the blood-brain barrier very slowly, eliminating the need for simultaneous measurement of blood lactate levels[11]. CSF lactates have also been used for prognostication, with rapidly falling levels shown to be associated with positive outcomes[26]. It is generally advised to obtain CSF for lactate measurement before administering antibiotics, as antibiotic exposure may reduce its sensitivity[27]. However, in our patient cohort, more than 90% of patients had already received antibiotics still the sensitivity and specificity of CSF lactate remained good.

The cut-off for CSF lactate still needs to be clarified, with different authors using different cut-offs ranging from 2-3 mmol/l[28,29]. Our study observed that CSF lactates had the best accuracy at the cut-off of 2.7 mmol/l, within the generally accepted range. Moreover, it is agreed that the higher the CSF lactates, the higher the chances of it being caused by bacterial meningitis. A meta-analysis by Huy et al. reported that a CSF lactate of ≥3.5 mmol/L was associated with a high sensitivity ranging from 96-99% and specificity ranging from 88-94% in diagnosing bacterial meningitis[26]. In our study, CSF lactate levels were also significantly higher in bacterial (8.85 ± 4.66 mmol/l) versus non-bacterial causes of meningitis (4.15 ± 3.84 mmol/l).

There are several strengths to our study. It was a nicely designed prospective study, and we included all the available measures, including CSF cultures and

PCR-based panels, to reach a diagnosis. Moreover, our study had primarily medically ill patients and was the first to show the correlation of CSF lactates with modern diagnostic techniques like PCR-based panels. The limitation of our study was that it was a monocentric study with a relatively small number of patients. Hence, it is imperative to conduct a larger multi-centre trial to improve the generalizability of our results.

CONCLUSIONS

CSF lactate may be used as an add-on marker to aid our clinical diagnosis of meningitis in critically ill patients. CSF lactate cut-off value above 2.72 mmol/L showed good accuracy, sensitivity, and specificity in diagnosing meningitis. High CSF lactates also help us to differentiate between bacterial and non-bacterial causes of meningitis and show a good correlation with CSF cultures and PCR-based meningoencephalitis for the diagnosis of meningitis.

1.	*normal glucose level and a normal to slightly elevated protein level*	Aseptic and Bacterial Meningitis: Evaluation, Treatment, and ... - AAFP https://www.aafp.org/pubs/afp/issues/2017/0901/p314.html	Originality
2.	*using the chi-square test or Fisher's exact test, as appropriate.*	Preoperative Serum Albumin Level as a Predictor of Abdominal Wound ... https://www.cureus.com/articles/107919-preoperative-serum-albumin-level-as-a-predictor-of-abdominal-wound-related-complications-after-emergency-exploratory-laparotomy	Originality
3.	*have been developed and are being increasingly used*	Reading and Understanding Patent Claims - The Minerals, Metals ... https://www.tms.org/pubs/journals/JOM/matters/matters-9511.html	Originality