Original Research Article

Clinical study of CSF lactate as a diagnostic marker to differentiate pyogenic meningitis from nonpyogenic meningitis at tertiary health care center

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Abstract

Background: The magnitude of this problem can be understood from the fact that over 1.2 million cases of bacterial meningitis are estimated to occur worldwide each year. Without treatment, the case-fatality rate can be as high as 70 percent, and one in five survivors of bacterial meningitis may be left with permanent sequel including hearing loss, neurologic disability, or loss of a limb. CSF lactate is produced by anaerobic metabolism and its level increases in any condition which causes decrease in oxygen supply to the brain. The diagnostic value of CSF lactate lies in the identification of untreated and partially treated bacterial meningitis. Present study was undertaken to determine the usefulness of CSF lactate as a diagnostic marker to differentiate pyogenic meningitis from nonpyogenic meningitis at tertiary health care center. **Material and Methods:** This prospective, observational study was conducted in department of Internal medicine in patients age > 18 years with fever, headache and signs of meningeal irritation with or without seizures and depressed level of consciousness. **Results:** In present study total 54 patients fulfilled inclusion and exclusion criteria. Most of the patients were above 50 years age group (48 %), age group 51-60 was most common age group. Male patients (59 %) were more than female patients (41 %). Male to female ratio was 1.25 :1. Fever, headache and altered sensorium were the most common presenting symptoms and majority of patients had signs of meningeal irritation. Most number of cases were pyogenic meningitis (56 %) while 44% were of non-pyogenic meningitis. The mean value of CSF lactate in pyogenic meningitis group were higher than non-pyogenic meningitis (136.51 ± 41.14 mg/dL vs. 34.18 ± 10.21 mg/dL). Statistically CSF lactate levels were significantly increased in pyogenic meningitis cases when compared to CSF lactate levels in non-pyogenic meningitis patients. **Conclusion:** CSF lactate level is markedly elevated in pyogenic meningitis as compared to non-pyogenic meningitis and it can be used to distinguish pyogenic meningitis from non-pyogenic meningitis.

Keywords: pyogenicmeningitis, pyogenic meningitis, CSF lactate.

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INTRODUCTION

The incidence of bacterial meningitis is 4 to 6 cases per 100,000 persons in the developed world, and the condition is at least 10 times more common in the developing world, where it is nearly uniformly fatal because of the limited availability of antibiotics.[1,2] The magnitude of this problem can be understood from the fact that over 1.2 million cases of bacterial meningitis are estimated to occur worldwide each year. Without treatment, the case-fatality rate can be as high as 70 percent, and one in five survivors of bacterial meningitis may be left with permanent sequel including hearing loss, neurologic disability, or loss of a limb.[3] The clinical presentation of bacterial meningitis is highly

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dependent on the immune response, and therefore, on the status of the host's innate immune system. It is influenced by age, immunocompromising conditions, and disruption of anatomic barriers. The clinical triad of meningitis, fever, neck stiffness, and altered mental status is, unfortunately, present in less than half of adult patients who have bacterial meningitis. Analysis of cerebrospinal fluid (CSF) remains the key to diagnosis. For identifying the cause of meningitis, clinical features, routine CSF parameters, and radiological findings are often inadequate. Gram's stain and AFB stain of CSF are the most common rapid methods of detection of the organism, however, these methods lack sensitivity. Culture of CSF is time-consuming. Although PCR and nowadays Real-time- PCR are extremely sensitive and specific tests for diagnosis, but are expensive and less available. Because of all these limitations, the determination of the CSF lactate level may be a diagnostic and invaluable marker in differentiating pyogenic/bacterial from nonpyogenic meningitis.[4] The goal of therapy remains the early administration of appropriate antibiotics, although in selected patients, adjuvant therapy with dexamethasone also may be administered. Delay in distinguishing between bacterial, viral and tubercular meningitis and treatment may have serious consequences that lead to significant morbidity and mortality.[5] Delay in seeking medical care, diagnosis, and initiation of treatment are contributing factors to the high mortality and morbidity, especially in resource limited regions. CSF lactate is produced by anaerobic metabolism and its level increases in any condition which causes decrease in oxygen supply to the brain. The diagnostic value of CSF lactate lies in the identification of untreated and partially treated bacterial meningitis. Intermediate levels of lactate is seen in the partially treated cases. The decrease in the lactate level is suggestive of a effective therapy and resolution of infection. The importance of CSF lactate level lies in its prognostic value in predicting the outcome of the patient.[6] Present study was undertaken to determine the usefulness of CSF lactate as a diagnostic marker to differentiate pyogenic meningitis from nonpyogenic meningitis at tertiary health care center.

MATERIAL AND METHODS

This prospective, observational study was conducted in department of Internal medicine, Department of General Medicine, Rajiv Gandhi Institute of Medical Sciences. Institutional ethical committee permission was obtained for this study. Study duration was of 1 year (January 2019 to January 2020). Informed consent was obtained from the patients or the attenders if the patient is sick enough to give the consent.

Inclusion criteria

Patients age > 18 years with fever, headache and signs of meningeal irritation with or without seizures and depressed level of consciousness.

Exclusion criteria

1. Patients with contraindications for lumbar puncture such as documented ICSOL, coagulopathy, local infection at sites of lumbar puncture,
2. patients with pyogenic infections elsewhere with tissue necrosis
3. Patients with malignancy
4. severe hepatic failure
5. patients on long term steroids and OCP,
6. patients with recent history of stroke

Patients admitted in department of Internal medicine with clinical syndrome suggestive of Acute meningitis such as fever, headache, neck stiffness, seizures, vomiting, altered sensorium, signs of meningism and focal neurologic deficit (blindness, double vision, hemiparesis, bulbar symptoms) regardless of their past treatment status were enrolled in present study. Past history of Diabetes, Tuberculosis and immunodeficient states and drug history, smoking, alcohol abuse and substance abuse, if any, was elicited. A detailed physical examination along with screening neurological examination was done to document the signs of meningeal irritation and to evaluate the focal neurological deficit. Complete blood count, random blood sugar, renal and liver function test, serum electrolytes, urine routine and ECG were done. Chest x ray was done to rule out the infective foci like pneumonia, Koch's. An urgent coagulation profile was performed to rule out coagulopathy. If there were no features coma on presentation, focal neurological deficit or immunocompromised state features, a lumbar puncture was performed without delaying unduly for imaging. The procedure was done after getting the informed consent. The sample was sent for cell count, cytology, protein, sugar, gram stain, AFB stain, lactate values and PCR (if clinically indicated). Separate sample was drawn with sterile precaution in a culture broth for culture and sensitivity. Emergent CT or MRI if needed, as dictated by clinical scenario, with contrast, was done to note the meningeal enhancement and to evaluate for the complications of meningitis. Data was collected and entered in Microsoft excel sheet. Statistical analysis was done using descriptive statistics.

Statistical methods such as Fischer's exact test were used for statistical analysis.

RESULTS

In present study total 54 patients fulfilled inclusion and exclusion criteria. Most of the patients were above 50 years age group (48 %), age group 51-60 was most common age

group. Male patients (59 %) were more than female patients (41 %). Male to female ratio was 1.25 :1. Fever, headache and altered sensorium were the most common presenting symptoms and majority of patients had signs of meningeal irritation.

Table 1: General characteristics

Characteristics	No of patients	Percentage
Age group		
19-30	8	15%
31-40	9	17%
41-50	11	20%
51-60	14	26%
More than 60	12	22%
Mean Age		
Gender		
Male	32	59%
Female	22	41%

Most number of cases were pyogenic meningitis (56 %) while 44% were of non-pyogenic meningitis.

Table 2: Incidence of type of meningitis

Type of meningitis	No of patients	Percentage
Pyogenic	30	56%
Non- Pyogenic	24	44%
Total	54	

The mean value of CSF lactate in pyogenic meningitis group were higher than non-pyogenic meningitis (136.51 ± 41.14 mg/dL vs. 34.18 ± 10.21 mg/dL). Statistically CSF lactate levels were significantly increased in pyogenic meningitis cases when compared to CSF lactate levels in non-pyogenic meningitis patients.

Table 3: CSF lactate levels

Group	*n*	Mean±SD
Pyogenic	30	136.51 ± 41.14
Non- Pyogenic	24	34.18 ± 10.21

DISCUSSION

CSF lactate is produced largely by the brain during normal anaerobic glycolysis by inter-conversion from pyruvate via the action of lactate dehydrogenase (LDH). In BM, there will be influx of inflammatory cells leading to global cerebral edema and hypoperfusion secondary to vasospasm, and loss of autoregulatory mechanism further leading to ischemia and anaerobic metabolism. In addition, the elevated CSF lactate level that commonly accompanies a low CSF glucose level strongly suggests that increased anaerobic metabolism contributes to these changes. Varying amount of lactate is produced by the bacteria itself accounting for 10% of total CSF lactate.[7] The mechanism of lactate production in brain is due to the meningitis associated cerebral ischemia and anaerobic metabolism. Unlike glucose, the blood lactate level will not influence the CSF lactate level and they are largely independent of each other since the CSF lactate level depends upon the local production in the brain. This is an advantage over the CSF glucose.[8,9] Conduction of the LP procedure in irritable and uncooperative patients can result in the collection of blood-stained CSF, and in these patients, the usual markers (especially the cell counts) are not dependable, whereas CSF lactate does not alter significantly with a changing plasma lactate level or CSF neutrophil and RBCs count. [10] Clues that can be used to supplement routine CSF analysis in diagnosing bacterial meningitis are an elevated CSF lactate (>4.2 mmol/L), serum c-reactive protein (CRP), and serum procalcitonin (PCT) concentration.[10] A study by Dash and Patro showed mean LDH 271.4 ± 80.07 mg/dl for pyogenic meningitis and 199.71 ± 74.16 mg/dl for tubercular meningitis.[11] Vekaria *et al.*.[12] also showed in their study that CSF LDH level increase maximally in pyogenic meningitis with a range of 35.5–750 u/l and mean 171.25u/l, mild increase LDH activity in viral meningitis (17–75 u/l, mean 35.6 u/l), and moderately increases in tubercular meningitis (20.4–315 u/l, mean 105.65 u/l). Sharma and Nand[13] showed that LDH level is significantly elevated in meningitis, the rise is more in pyogenic meningitis (260 ± 110.96) than in tubercular meningitis (190.48 ± 65.49) as compared to control (20.64 ± 3.63). Another study by Banik A *et al.*[14] noted that, mean CSF LDH are 280.94 ± 74.488 mg/dl (95% CI: 261.60–300.48) for pyogenic meningitis, 171.24 ± 211.58 mg/ dl (95% CI: 171.24–211.58) for tubercular meningitis, and 35.60 ± 10.394 mg/dl (95% CI: 32.58–38.36) for viral meningitis. This difference between CSF LDH is statistically significant between all groups. Two meta-analyses were performed on the diagnostic use of CSF lactate in the differentiation of bacterial meningitis vs. other types of meningitis. One included 25 studies with 1692 patients[15], and the other included 31 studies with 1885 patients[16]. These meta-analyses concluded that the diagnostic accuracy of CSF lactate is better than that of CSF WBC count. In patients who received antibiotic treatment before lumbar puncture, CSF lactate concentration had a lower sensitivity (49%) compared to those not receiving antibiotic pretreatment (98%). Lactate in CSF has been shown to be better than CSF WBC to discriminate between bacterial and aseptic meningitis, a sensitivity of 93% and specificity of 98% was reported.[15,16] CSF lactate concentrations are also useful for the diagnosis of post surgical acute bacterial meningitis, where there is not an increase in specific cells or proteins.[17] The important implication of CSF lactate level determination in the clinical use lies in the prompt discrimination between the viral meningoencephalitis (<3 mmol/L) and pyogenic meningitis-both partially treated (>3-6 mmol/L) and untreated cases (>6mmol/L).[18] The finding of minimal elevation of around 2 to 4 mmol/L is not to be confused with the pyogenic meningitis. The explanation for this mild

elevation is given as the presence of RBC s in the CSF which accompanies the hemorrhagic necrosis of HSV encephalitis which may cause elevation of lactate levels but only slightly unlike pyogenic meningitis associated lactate levels.[19] The clinical course of the pyogenic meningitis patients can be known from the lactate levels. The prognostic status of the patients can be deciphered from CSF lactate level and it can predict those who are likely to recover with or without sequelae and also the risk of mortality.[18] In addition to its diagnostic value, CSF lactate is also helpful as a good prognostic indicator, showing a rapid decline after the initiation of antibiotics.[20] While some other authors had found different results. An elevated CSF lactate concentration is an exquisitely sensitive test for acute bacterial meningitis; unfortunately, its clinical utility is limited since it can be elevated for other reasons, such as cerebral hypoxia/ischemia, anaerobic glycolysis, vascular compromise, and metabolism of CSF leukocytes.[5] CSF lactate concentration is less accurate for differentiating patients with other central nervous system diseases from meningitis, such as herpes encephalitis or seizures, as the concentrations may also be raised.[21] Therefore, the usefulness of CSF lactate concentrations in patients pretreated with antibiotics, or those with other central nervous system diseases in the differential diagnosis, is probably limited.

CONCLUSION

An immediate and accurate diagnosis of acute meningitis is the most important factor in treatment as bacterial meningitis is associated with significant mortality and morbidity in the form of permanent neurological deficits. CSF lactate level is markedly elevated in pyogenic meningitis as compared to non-pyogenic meningitis and it can be used to distinguish pyogenic meningitis from non-pyogenic meningitis.

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