International Journal of Health Sciences and Research
Vol.10; Issue: 8; August 2020
Website: www.ijhsr.org
ISSN: 2249-9571
Original Research Article

CSF Lactate - An Independent and Reliable Biomarker among the CSF Parameters to Differentiate Bacterial Meningitis from Aseptic Meningitis

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ABSTRACT

The objective of this study was to compare the mean values of CSF parameters (lactate, protein, sugar, ADA) and thereby distinguish between cases of bacterial and non-bacterial meningitis. A cross sectional study was conducted in which 60 adult patients were included and CSF parameters (differential counts, protein, sugar, ADA, lactate) were analyzed in 22 patients of bacterial meningitis and 38 patients of aseptic meningitis. Data were analyzed using SPSS version 21.0. Analytical statistics were represented using Chi-square test for the comparison of categorical variables. The mean values were compared using independent t- test. Among the other CSF parameters, the mean value of CSF lactate and CSF sugars were found to have significant difference (p-value 0.01) in bacterial and non-bacterial meningitis. However other parameters including CSF protein and CSF ADA did not show significant difference between bacterial meningitis including TBM and non-bacterial meningitis. This study concluded that CSF lactate is an important, independent and reliable biomarker with a cut off value of 3mmol/L, to differentiate bacterial meningitis including TBM from nonbacterial meningitis. TBM and viral meningitis are difficult to differentiate due to their similar clinical features and lab parameters. In such cases, CSF lactate can be taken as a reliable differentiating marker. CSF lactate can be used when CSF gram stain and cultures are inconclusive and time consuming. Thus, helps in initiating early treatment and achieving better outcomes.
Key Words: CSF lactate, CSF parameters, reliable and independent marker, aseptic meningitis

INTRODUCTION

Meningitis is one of the serious medical conditions which caused high mortality and morbidity. At the same time, early diagnosis and treatment can produce a good quality of life. Even with the advancement in molecular technology, the diagnosis is continued to be a medical challenge. A combination of present CSF variables (proteins, glucose, leucocytes count, and the ratio of CSF/serum glucose) has been suggested effective in differentiating non-bacterial meningitis from bacterial meningitis. [(1,2)] However, there are serious limitations of the above variables in diagnosing and differentiating bacterial and non-bacterial meningitis. [(1)] The CSF lactate concentration has been suggested as a useful parameter to differentiate bacterial from aseptic meningitis. Meningitis is one of the reasons for prolonged hospitalization. Considering the huge disease burden, there is a necessity of a cost-effective and reliable marker. CSF lactate is one such marker. CSF lactate in bacterial meningitis originates from different sources. Bacterial pathogens themselves produce varying amounts of lactate; accounting for 10% of the total CSF lactate. [1,3] Bacterial meningitis is associated with generalized brain edema, causing a reduction of global cerebral blood flow and inflammatory involvement of vasculature, with loss of autoregulatory mechanisms, vasospasm, and thrombosis. This leads to cerebral ischemia and consequently to glycolysis by means of anaerobic metabolism. [1,4] In addition, cytokines that flood the brain in meningitis reduce tissue oxygen uptake and causes a shift toward anaerobic metabolism, thus increasing lactate production. Cytokines also mediate invasion of neutrophils into the subarachnoid space, which may also contribute to the rise in CSF lactate level by glycolysis in bacterial meningitis. [1,5] Tubercular meningitis (TBM) is the most serious form of neurotuberculosis. India is among the nations with a high incidence of TB. Usually, there are 20% of extrapulmonary cases of which, 15% are neurotuberculosis. [6] CSF lactate level is easy to estimate and cost-effective. There are few studies that addressed the diagnostic value of the CSF lactate in bacterial meningitis or differentiating bacterial from viral meningitis and tuberculous meningitis. This study aimed to compare the mean values of CSF parameters (Lactate, protein, sugar, ADA) and thereby distinguish between cases of bacterial and non-bacterial meningitis.

MATERIALS AND METHODS

A cross-sectional study conducted in the Department of General Medicine and the Department of Neurology at Amrita Institute of Medical Sciences, Kochi, Kerala including 60 adult patients above 18 years with clinical features of meningitis for a period of 18 months (November 2018 to May 2020) while patients with coagulopathy, mitochondrial diseases, and pregnant patients were excluded. The study was approved by the institutional ethical committee and informed consent was taken from the patients. The sample size required with 80 % power and 99.9% confidence was 4 per group. However, the authors could analyze 60 patients in the mentioned study period. History and physical examination were recorded in the study proforma. The CSF sample was collected on the first spinal tap conducted in the institution. CSF lactate estimation was done using the calorimetric method. Based on the other biochemical analysis, patients were further divided into two groups.

• Group A patients had clinical symptoms including fever, headache, and signs of meningeal irritation. Criteria for pyogenic meningitis included CSF analysis showing neutrophilic predominant pleocytosis with elevated CSF protein(45mg/dl)and low CSF glucose(<40mg/dl) whereas criteria for TBM included CSF analysis showing lymphocytic predominant high protein(>100mg/dl),low glucose, CSF GeneXpert positivity and features like basal exudates and tuberculoma in neuroimaging. The rest of the patients were categorized into group B.

Data were analyzed using SPSS version 21.0. Descriptive statistics were represented using frequencies and percentages. Analytical statistics were represented using Chi-square test for the comparison of categorical variables. Independent sample T-test was applied for comparing the mean CSF lactate level between bacterial and nonbacterial meningitis.

RESULTS

Table 1: Distribution of study population across different age groups

Age Category	Frequency	Percent
20 years	2	3.3
21- 40 years	12	20
41 – 60 years	24	40
Above 60 years	22	36.7
Total	60	100.0

During the study period, 60 patients were included in the study. 40 percent of the study population was between 41- 60 years of age with 37 males and 23 females. Based on the CSF biochemical parameters, 22 patients had bacterial meningitis and 38 patients had nonbacterial meningitis. The cut off value of CSF lactate and CSF sugars were taken as 3mmol/L and 80mg/dl, respectively. Based on this; the patients were divided into two categories. CSF lactate was elevated in 16 cases of bacterial meningitis and 8 cases of non-bacterial meningitis. CSF Glucose was reduced in 20 cases of bacterial meningitis and 17 cases of non-bacterial meningitis. CSF protein and CSF ADA were found to have no association with bacterial meningitis including TBM. The CSF lactate and CSF sugars in bacterial meningitis differed significantly from aseptic meningitis (p value <0.01). Among the two, it was found out that CSF lactate showed more significance. Also, the mortality rate increased with increasing lactate levels.

Table 2: Distribution of the study population based on Gender

Category	Frequency	Percent
Male	37	61.6
Female	23	63.3
Total	60	100.0

Table 3: Distribution of the study population based on diagnosis

Category	Frequency	Percent
Bacterial Meningitis	22	36.7
Non-Bacterial Meningitis	38	63.3
Total	60	100.0

Table 4: Distribution of the study population based on mortality

Category	Diagnosis		Total
	Bacterial meningitis	Nonbacterial meningitis	
Mortality-No	14	34	48
Mortality-Yes	8	4	12
Total	22	38	60

Table 5: Distribution of study population according to various CSF parameters

Category	Frequency	Percent
1. CSF LACTATE LEVELS		
• Lactate levels below 3 mmol/L	36	60
• Lactate levels above or equal to 3 mmol/L	24	40
2. CSF SUGAR LEVELS		
• Sugar levels below or equal to 80 mg/dL	37	61.7
• Sugar levels above 80 mg/dL	23	38.3
3. CSF PROTEIN LEVELS		
• CSF Protein levels below or equal to 40 mg/dL	23	38.3
• CSF Protein levels above 40 mg/dL	37	61.7
4. ADA LEVELS		
• CSF ADA levels below or equal to 2.8 IU/L	51	85
• CSF ADA levels above 2.8 IU/L	9	15
5. DIFFERNTIAL CELLS		
• Mononuclear cells	46	76
• Segmented cells	14	23

Table 6: Distribution of study population according to the CSF lactate levels

Category	DIAGNOSIS		TOTAL	Chi-Square (p-value)	Odds ratio (Confidence interval limits)
	Bacterial Meningitis	Non-Bacterial Meningitis			
CSF Lactate levels below 3 mmol/L	6	30	36	15.502 (<0.01)	0.1 (0.03-0.33)
CSF Lactate levels above or equal to 3 mmol/L	16	8	24		

Table 7: Distribution of study population according to the CSF sugar levels

Category	DIAGNOSIS		TOTAL	Chi-Square (p-value)	Odds ratio (Confidence interval limits)
	Bacterial Meningitis	Non-Bacterial Meningitis			
CSF Sugar levels below or equal to 80 mg/dL	20	17	37	12.56 (<0.01)	12.35 (2.52-60.45)
CSF Sugar above 80 mg/dL	2	21	23		

Table 8: Distribution of study population according to the CSF protein levels:

Category	DIAGNOSIS		TOTAL	Chi-Square (p-value)	Odds ratio (Confidence interval limits)
	Bacterial Meningitis	Non-Bacterial Meningitis			
CSF Protein levels below or equal to 40 mg/dL	4	19	23	5.96 (0.15)	0.22 (0.06-0.78)
CSF Protein levels above 40 mg/dL	18	19	37		

Table 9: Distribution of study population according to the CSF ADA levels

Category	DIAGNOSIS		TOTAL	Chi-Square (p-value)	Odds ratio (Confidence interval limits)
	Bacterial Meningitis	Non-Bacterial Meningitis			
CSF ADA levels below or equal to 2.8 IU/L	18	34	52	0.707 (0.401)	0.529 (0.11-2.37)
CSF ADA levels above 2.8 IU/L	4	4	8		

Table 10: Distribution of study population according to Differential counts

Category	Bacterial Meningitis	Non-Bacterial Meningitis	TOTAL	Chi-Square (p-value)	Odds ratio (Confidence interval limits)
Mononuclear cells	8	38	46	31.54 (0.01)	0.17 (0.09-0.032)
Segmented cells	14	0	14		

Table 11: Distribution of study population according to the Mortality

Category	Bacterial Meningitis	Nonbacterial Meningitis	Total	Chi- Square (p value)	Odds ratio (Confidence interval limits)
Mortality-No	14	34	48	5.81 (<0.01)	0.2 (0.503-0.796)
Mortality-Yes	8	4	12		

DISCUSSION

The therapeutic decision-making of bacterial meningitis is critical due to the highly significant disease associated mortality and morbidity. In our study, we found that CSF lactate is the most prominent biomarker for diagnosing bacterial meningitis. It was also found that lactate concentration increases proportionally to the number of inflammatory cells in CSF. A lactate concentration of 4.2 mmol/L accurately predicted 24 out of 25 bacterial meningitis as per literature. [7,8] Unlike glucose, CSF lactate typically remains elevated for a significant time even if after appropriate therapy is initiated. This may help in diagnosing bacterial meningitis, in which antibiotics had been given already. [7,9] Smith et al have reported, CSF lactate as a useful tool in the early diagnosis of bacterial meningitis with high sensitivity (92%) and specificity (99%) as well as in differentiating bacterial from viral meningitis. Klein et al. have also reported that the CSF lactate level has higher reliability than the opposite CSF tests in diagnosing and differentiating bacterial meningitis from viral meningitis. It was also noticed that patients who died had higher CSF lactate level (avg.19.4 mmol/L) than those who were discharged with or without sequelae, an observation which is also reported by the other investigators. [1,11,12,13] Another study by Curtis GD et al., observed that in 109 patients of proven bacterial meningitis, the mean lactate concentration was elevated (over 2.8 mol l-1) in all cases. [6,10] Zebba Siddiqi et al. reported that CSF lactate had a positive association with both the stage and diagnostic class of TBM than CSF ADA. In this study, there was a significant difference in the CSF lactate among bacterial and nonbacterial meningitis with a p- value of 0.01.

CONCLUSION

This study concludes that CSF lactate is an important, independent and reliable biomarker with a cut off value of 3mmol/L, to differentiate bacterial meningitis including TBM from nonbacterial meningitis. TBM and viral meningitis are difficult to differentiate due to their similar clinical features and lab parameters. In such cases, CSF lactate can be taken as a reliable differentiating marker. CSF lactate can be used when CSF gram stain and cultures are inconclusive and time consuming. Thus, helps in initiating early treatment and achieving better outcomes.

Limitation

The main limitation of the study was a small sample size and the risk prediction is limited due to the small sample size. Also, the study was not compared to gold standard method of diagnosis.

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How to cite this article: Remash K, Raj R, Pillai MGK et.al. CSF Lactate - an independent and reliable biomarker among the CSF parameters to differentiate bacterial meningitis from aseptic meningitis. Int J Health Sci Res. 2020; 10(8):1-5.

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