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Research Article

A study on importance of lactate levels in cerebrospinal fluid to differentiate bacterial from aseptic meningitis

Zeeshan Qayyum, Muhammad Ahsan Aziz and Hashir Amin Malik

[1]Medical Officer RHC Kala, Dera Ghazi khan
[2]Medical Officer, BHU 133/ml, DistrictMuzafargarh, Tehsil Kotadu
[3]Medical Officer, Cardiac Centre Chunian

ABSTRACT

Objective: To determine the diagnostic accuracy of CSF lactate levels in differentiating bacterial and viral meningitis, taking CSF culture as gold standard.
Study design: Descriptive, Cross Sectional study.
Setting:RHC KalaDera Ghazi khan
Duration of study: January 2017 to June 2017
Materials & Methods: A total of 126 patients of with suspicion of meningitis, age 10-40 of both genders were included. Patients with h/o antibiotics intake, immunosuppressive therapy, tuberculosis, recent stroke, subarachnoid hemorrhage or seizures and brain trauma were excluded. Cerebrospinal fluid lactate levels were measured in every patient. Patients were diagnosed as having bacterial or viral meningitis on the basis of CSF lactate levels (≥3.8 mmol/L was considered as bacterial meningitis and <3.8 mmol/L was considered as viral meningitis). CSF lactate diagnosis was correlated with CSF culture findings.
Results: Mean age was 26.47 ± 8.13 years. Out of 126 patients, 74 (58.73%) were males and 52 (41.27%) were females with male to female ratio of 1.4:1. CSF lactate levels supported the diagnosis of bacterial meningitis in patients 81 (64.29%). CSF culture confirmed bacterial meningitis in 83 (65.87%) cases. In 81 CSF lactate levels positive patients, 75 (True Positive) had bacterial meningitis and 06 (False Positive) had viral meningitis on CSF culture. Among, 35 CSF lactate levels negative patients, 08 (False Negative) had bacterial meningitis on CSF culture where as 37 (True Negative) had viral meningitis on CSF culture. Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CSF lactate levels in differentiating bacterial and viral meningitis was 90.36%, 86.05%, 92.59%, 82.22% and 88.89% respectively.
Conclusion: This study concluded that CSF lactate levels have high sensitivity and specificity in differentiating bacterial and viral meningitis and shouldbe used routinely in our general practice in differentiating meningitis.

Keywords: meningitis, CSF parameters, lactate, bacterial.

INTRODUCTION

Meningitis is an acute inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges.[1] The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs.[2] Despite the advances in diagnosis and treatment of infectious diseases, meningitis is still considered as an important cause of mortality and morbidity, especially in the pediatric population.[3] The types of bacteria that cause bacterial meningitis vary according to the infected individual's age group. In premature babies and newborns up to three months old, common causes are group B

streptococci and bacteria that normally inhabit the digestive tract such as Escherichia coli. Listeria monocyto genes (serotype IVb) may affect the newborn and occurs in epidemics.[4]

Older children are more commonly affected by Neisseria meningitidis (meningococcus) and Streptococcus pneumoniae (serotypes 6, 9, 14, 18 and 23) and those under five by Haemophilusinfluenzae type B (in countries that do not offer vaccination).[4,5] In adults, Neisseria meningitidis and Streptococcus pneumoniae together cause 80% of bacterial meningitis cases. Risk of infection with Listeria monocytogenes is increased in persons over 50 years old.[6,7] The introduction of pneumococcal vaccine has lowered rates of pneumococcal meningitis in both children and adults.[8]

Bacterial meningitis (BM) can cause serious complications and its severity depends not only on the causal microorganism, but also on host immune factors, immunization status, and geographic region.[9]Abro AH et al[10] in his study has shown the prevalence of bacterial meningitis in 64% patients presenting with meningitis. Accurate and rapid diagnosis of acute bacterial meningitis (BM) is essential because disease outcome depends on immediate initiation of appropriate antibiotic therapy. BM should be treated promptly with antibiotics, whereas acute aseptic meningitis (AM) is usually self limiting.[11]

Bacterial meningitis has a lengthy differential diagnosis, including numerous infectious disease and noninfectious disease mimics. Clinical manifestations, patient age, and presence of co-morbid conditions can provide diagnostic clues. Clinical features can also help in predicting disease outcome. Cerebrospinal fluid examination findings, including Gram stain and culture results, are important for accurate diagnosis.[12] When bacterial meningitis is suspected, early empiric therapy is called for; selection of antibiotic agents for empiric therapy must take epidemiologic trends into consideration. Choice of specific drugs for confirmed bacterial meningitis and length of treatment are determined by the causative organism. Use of adjunctive corticosteroids may improve outcomes.[13]

Differentiating acute bacterial and viral meningitis is not always easy. Combination of present CSF variables (proteins, glucose, leucocytes count and ratio of CSF/serum glucose) has been suggested effective in differentiating acute viral meningitis from bacterial meningitis.[14] However, there are serious limitations of the above variables in diagnosing and differentiating bacterial and viral meningitis. The CSF lactate concentration has been suggested as a useful parameter to differentiate bacterial from viral meningitis.[15]

Lactate is a hydroxycarboxylic acid and exists in the human bodyas two stereoisomers, L-lactate and D-lactate. L-lactate is the majorphysiological enantiomer of lactate in the human body and has beentraditionally considered to contribute to metabolic acidosis.[16] Undernormal physiological condition, D-lactate is also present in the humanbody but only at low concentrations, accounting for 1–5% of Llactate.[17] Under anaerobic conditions, bacteria produced D-lactate andLlactate.[18,19] It showed that the human cells are only capableof producing Llactate, while bacteria can produce Dand Llactate.If a considerable proportion of lactate in the CSF is produced by bacteriathen Dlactate would be an ideal indicator for diagnosing BM since it iseasy to measure. Viallon A et al[20] in his study has found the sensitivity of 94% and specificity of 92%, at a diagnostic cut-off level of 3.8 mmol/L of CSF lactate levels in diagnosing bacterial from viral meningitis.

As bacterial meningitis is an infectious disease with significant morbidity and mortality if accurate and timely diagnosis could not be made and early treatment could not be started. So, there was a need of a rapid diagnostic test with high diagnostic accuracy for differentiating bacterial from viral meningitis. In this issue, CSF lactate could be helpful but data available on this was very scarce and moreover, no local study was available on this, so we had planned to conduct a study to determine the diagnostic accuracy of

CSF lactate levels in differentiating bacterial from viral meningitis in our population. Then based on these results, we could opt this test in our routine practice guidelines for early diagnosis and timely management of this devastating condition in order to reduce the morbidity and mortality of our community.

OPERATIONAL DEFINITIONS:

1. **Meningitis:** presence of all of the following was considered positive;
   a. Vomiting.
   b. Fever (>100 F).
   c. **Nuchal rigidity:** the inability to flex the neck forward passively due to increased neck muscle tone and stiffness.
   d. **Positive Kernig's sign:** was assessed with the person lying supine, with the hip and knee flexed to 90 degrees. In a person with a positive Kernig's sign, pain will limit passive extension of the knee.
   e. **Positive Brudzinski's sign**: was occurred when flexion of the neck causes involuntary flexion of the knee and hip.
   f. **CSF examination**: has shown neotrophilicpleocytosis (>10 cells/mm^3), raised proteins (>45 mg/dl), low sugars (<40 mg/dl).
2. **CSF Lactate levels:** if CSF lactate levels were be ≥3.8 mmol/L then it was considered as bacterial meningitis and if <3.8 mmol/L, then it was considered as viral meningitis.
3. **True Positive:** Patients with bacterial meningitis on CSF lactate levels who had positive CSF culture for bacteria.
4. **True negative:** Patients with no bacterial meningitis on CSF lactate levels who had also negative CSF culture for bacteria.
5. **False Positive:** Patients with bacterial meningitis on CSF lactate levels who had negative CSF culture for bacteria.
6. **False Negative:** Patients with no bacterial meningitis on CSF lactate levels who had positive CSF culture for bacteria.
7. **Diagnostic Accuracy:** was measured in terms of;

a. **Sensitivity** = $\frac{TP}{\text{All positive cases on CSF culture}}$ x 100

b. **Specificity** = $\frac{TN}{\text{All negative cases on CSF culture}}$ x 100

c. **Positive Predictive Value (PPV)** = $\frac{TP}{\text{All positive cases on CSF lactate levels}}$ x 100

d. **Negative Predictive Value** = $\frac{TN}{\text{All negative cases on CSF lactate levels}}$ x 100

MATERIAL AND METHODS

Study design: Descriptive, Cross-sectional study.

Setting: RHC KalaDera Ghazi Khan

Duration of study: January 2017 to June 2017

Inclusion Criteria:

a. All patients with suspicion of meningitis as per-operational definition.
b. Patients 10-40 years of age.
c. Both genders.

Exclusion Criteria:

a. Patients with h/o antibiotics intake.
b. Patients with h/o immunosuppressive therapy.
c. Patients with h/o tuberculosis.
d. Patients with h/o recent stroke, subarachnoid hemorrhage or seizures.
e. Patients with h/o brain trauma.
f. Patients not willing to be included in the study.

Data collection procedure:

After permission from local ethical review committee, total number of 126 patients who were admitted at RHC Kala Dera Ghazi Khan fulfilling the inclusion/exclusion criteria were selected. After taking informed consent and relevant history, cerebrospinal fluid (CSF) lactate levels were measured in CSF of every patient by same consultant pathologist (with at least 3 years of post-fellowship experience). Patients were diagnosed as having bacterial or viral meningitis

on the basis of CSF lactate levels as described in operational definition. CSF lactate diagnosis was correlated with CSF culture findings. All this data was recorded on a specially designed proforma.

Data analysis procedure:

Collected data was analyzed through computer software SPSS 20.0. Mean and standard deviation was calculated for quantitative variables i.e. age, duration of disease and CSF lactate levels. Frequency and percentage was calculated for qualitative variables i.e. gender, bacterial and viral meningitis. 2×2 contingency table was used to calculate sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CSF lactate levels in differentiating bacterial and viral meningitis taking CSF culture as gold standard. Effect modifiers like age, gender and duration of disease was controlled by stratification. Post-stratification chi square was applied and p-value ≤0.05 was considered as significant.

RESULTS

Age range in this study was from 10-40 years with mean age of 26.47 ± 8.13years. Majority of the patients 48 (38.10%) were between 21 to 30 years of age as shown in Table I. Out of 126 patients, 74 (58.73%) were males and 52 (41.27%) were females with male to female ratio of 1.4:1 as shown in Figure I. Mean duration of disease was 19.72 ± 9.42hours.

CSF lactate levels supported the diagnosis of bacterial meningitis in patients 81 (64.29%). CSF culture confirmed bacterial meningitis in 83 (65.87%) cases where as 43 (34.13%) patients revealed viral meningitis. In 81 CSF lactate levels positive patients, 75 (True Positive) had bacterial meningitis and 06 (False Positive) had viral meningitis on CSF culture. Among, 35 CSF lactate levels negative patients, 08 (False Negative) had bacterial meningitis on CSF culture where as 37 (True Negative) had viral meningitis on CSF culture as shown in Table II.

Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CSF lactate levels in differentiating bacterial and viral meningitis was 90.36%, 86.05%, 92.59%, 82.22% and 88.89% respectively (Figure II). Stratification of diagnostic accuracy with respect to age groups has shown in Table III, IV & V while Table VI & VII have shown the stratification of diagnostic accuracy with respect to gender. Stratification of diagnostic accuracy with respect to duration of disease is shown in Table VIII & IX.

Table-I: %age of patients according to Age distribution (n=126).

Age (years)	No. of Pateints	%age
10-20	33	26.19
21-30	48	38.10
31-40	45	35.71
Total	126	100.0

Figure I: %age of patients according to gender

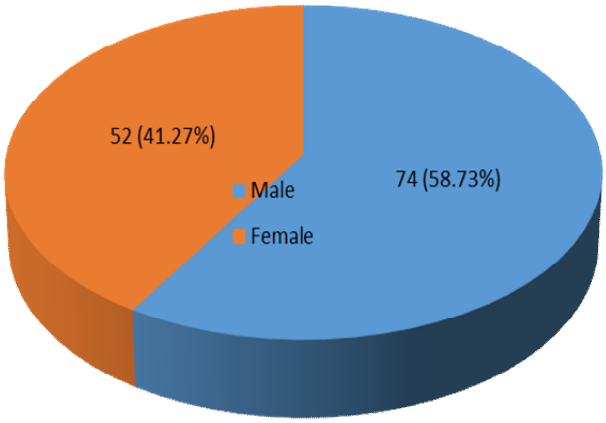

Table-II: Summary of Results.

	Positive on CSF Lactate Levels	Negative on CSF Lactate Levels	P-value
Positive on CSF Culture	75 **(TP)***	08 **(FN)*****	**0.791**
Negative on CSF Culture	06 **(FP)****	37 **(TN)********	

*-TP=True positive **-FP=False positive ***-FN=False negative ****-TN=True negative

Figure-II: Diagnostic accuracy of CSF lactate levels in differentiating bacterial and viral meningitis.

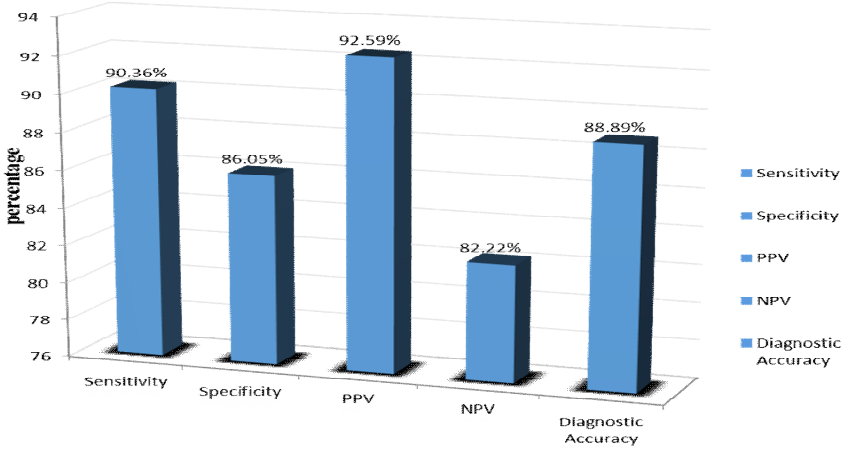

Table III: Stratification of age 10-30 years (n=33).

	Positive on CSF Lactate Levels	Negative on CSF Lactate Levels	P-value
Positive on CSF Culture	15 **(TP)**	00 **(FN)**	**0.805**
Negative on CSF Culture	01 **(FP)**	17 **(TN)**	

Sensitivity: 100.0%, **Specificity:** 94.44%, **Positive Predictive Value (PPV):** 93.75%, **Negative Predictive Value (NPV):** 100.0%, **Diagnostic Accuracy:** 96.97%

Table IV: Stratification of age 21-30 years (n=48).

	Positive on CSF Lactate Levels	Negative on CSF Lactate Levels	P-value
Positive on CSF Culture	31 **(TP)**	05 **(FN)**	**0.646**
Negative on CSF Culture	03 **(FP)**	09 **(TN)**	

Sensitivity: 86.11%, **Specificity:** 75.0%, **Positive Predictive Value (PPV):** 91.18%, **Negative Predictive Value (NPV):** 64.29%, **Diagnostic Accuracy:** 83.33%

Table V: Stratification of age 31-40 years (n=45).

	Positive on CSF Lactate Levels	Negative on CSF Lactate Levels	P-value
Positive on CSF Culture	29 **(TP)**	03 **(FN)**	**0.818**
Negative on CSF Culture	02 **(FP)**	11 **(TN)**	

Sensitivity: 90.63%, **Specificity:** 84.62%, **Positive Predictive Value (PPV):** 93.55%, **Negative Predictive Value (NPV):** 78.57%, **Diagnostic Accuracy:** 88.89%

Table VI: Stratification of Male gender (n=74).

	Positive on CSF Lactate Levels	Negative on CSF Lactate Levels	P-value
Positive on CSF Culture	55 **(TP)**	04 **(FN)**	**0.690**
Negative on CSF Culture	02 **(FP)**	13 **(TN)**	

Sensitivity: 93.22%, **Specificity:** 86.67%, **Positive Predictive Value (PPV):** 96.49%, **Negative Predictive Value (NPV):** 76.47%, **Diagnostic Accuracy:** 91.19%

Table VII: Stratification of Female gender (n=52).

	Positive on CSF Lactate Levels	Negative on CSF Lactate Levels	P-value
Positive on CSF Culture	20 **(TP)**	04 **(FN)**	**1.000**
Negative on CSF Culture	04 **(FP)**	24 **(TN)**	

Sensitivity: 83.33%, **Specificity:** 85.71%, **Positive Predictive Value (PPV):** 83.33%, **Negative Predictive Value (NPV):** 85.71%, **Diagnostic Accuracy:** 84.62%

Table VIII: Stratification of duration of disease ≤24 hours (n=67).

	Positive on CSF Lactate Levels	Negative on CSF Lactate Levels	P-value
Positive on CSF Culture	38 **(TP)**	05 **(FN)**	**0.858**
Negative on CSF Culture	04 **(FP)**	20 **(TN)**	

Sensitivity: 88.37%, **Specificity:** 83.33%, **Positive Predictive Value (PPV):** 90.48%, **Negative Predictive Value (NPV):** 80.0%, **Diagnostic Accuracy:** 86.57%

Table IX: Stratification of duration of disease >24 hours (n=59).

	Positive on CSF Lactate Levels	Negative on CSF Lactate Levels	P-value
Positive on CSF Culture	37 **(TP)**	03 **(FN)**	**0.845**
Negative on CSF Culture	02 **(FP)**	17 **(TN)**	

Sensitivity: 92.50%, **Specificity:** 89.47%, **Positive Predictive Value (PPV):** 94.87%
Negative Predictive Value (NPV): 85.0%, **Diagnostic Accuracy:** 91.53%

DISCUSSION

We have conducted this study to determine the diagnostic accuracy of CSF lactate levels in differentiating bacterial and viral meningitis, taking CSF culture as gold standard.In our study, CSF lactate levels supported the diagnosis of bacterial meningitis in patients 81 (64.29%). CSF culture confirmed bacterial meningitis in 83 (65.87%) cases where as 43 (34.13%) patients' revealed viral meningitis. In 81 CSF lactate levels positive patients, 75 (True Positive) had bacterial meningitis and 06 (False Positive) had viral meningitis on CSF culture. Among, 35 CSF lactate levels negative patients, 08 (False Negative) had bacterial meningitis on CSF culture where as 37 (True Negative) had viral meningitis on CSF culture. Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CSF lactate levels in differentiating bacterial and viral meningitis was 90.36%, 86.05%, 92.59%, 82.22% and 88.89% respectively in our study. Abro AH et al[10] in his study has found the mean CSF lactate level in bacterial meningitis cases as 14.96 ± 6.13 mmol/L with sensitivity of 98.3% and positive predictive value of 73.4%.

The study done by Gastrin B et al[21] have also supported that CSF lactate is a useful tool in the early diagnosis of bacterial meningitis as well as in differentiating bacterial from viral meningitis with sensitivity of 97.0% and specificity of 82.0%. Genton B et al[22] has endorsed the idea that the measurement of the CSF lactate is worth performing when meningitis is suspected, as it appeared to be the best way of distinguishing bacterial from non-bacterial meningitis and it has the high sensitivity (95%), specificity (100%) and predictive value (96%). However, Robert L et al[23] in his study suggested that the lactate level in the cerebrospinal fluid did not provide unequivocal evidence of bacterial infection and did not gave assistance to any greater degree than the standard parameters of leukocyte count, protein and glucose contents in the differential diagnosis of bacterial meningitis from that of any other etiology.

Kleine TO et al[24] has shown the sensitivity and specificity of CSF lactate levels in differentiating bacterial from aseptic meningitis as 100% and 100% respectively. On the other hand, Schwarz S et al[25] in his study has found 94% sensitivity and 43 specificity. Viallon A et al[20] in his study has found the sensitivity of 94% and specificity of 92%, at a diagnostic cut-off level of 3.8 mmol/L of CSF lactate levels in diagnosing bacterial from viral meningitis. In a meta-analysis done by Huy NTet al[11], the pooled sensitivity ranged from 0.86 to 1.00 (mean, 0.96; 95% confidence interval (CI), 0.95 to 0.98), while the pooled specificity varied widely from 0.43 to 1.00 (mean, 0.94; 95% CI, 0.93 to 0.96).

CONCLUSION

This study concluded that CSF lactate levels is a rapid performing, highly sensitive and accurate method for differentiating bacterial and viral meningitis, and has not only dramatically improved our ability of diagnosing bacterial meningitis but also provide the clinicians with a method for early diagnosis of this condition. So, we recommend that CSF lactate levels should be used routinely in our general practice for rapid, accurate and early diagnosis of bacterial meningitis which will result in its early and proper treatment in these particular patients in order to reduce their morbidity and mortality.

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