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Usefulness of CSF Lactate as a Diagnostic Marker to Differentiate Pyogenic Meningitis from Non-Pyogenic Meningitis: An Analytical Study

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Abstract

Aim: The aim of the present study was to determine the usefulness of CSF lactate as a diagnostic marker to differentiate pyogenic meningitis from non-pyogenic meningitis.

Methods: A hospital based one-year prospective study was conducted in the Department of General Medicine (Emergency) for one year. Total of 50 cases of meningitis which were diagnosed upon clinical evaluation were included in the study.

Results: Meningitis was common in the age group 51-60 (26%). Male patients (60%) were more than female patients (40%). Most number of cases was pyogenic meningitis (58%) while 42% were of non-pyogenic meningitis. Statistically CSF lactate levels were significantly increased in pyogenic meningitis cases when compared to CSF lactate levels in non-pyogenic meningitis patients. Fever was the most common symptom (92%) followed by vomiting (74%), headache (72%) and altered sensorium in 62% of cases. Brudzinski's sign was observed in 70% of cases and neck stiffness in 64%, kernig's sign in 58% and nerve palsies in 18% of cases. The mean total cell count was highest in cases of pyogenic meningitis with a mean of 842.88 and SD of 115.25 than viral and tubercular meningitis. However no statistical significance was associated with total count and types of meningitis. ('p' value -0.082) A clear neutrophil predominance was observed in all cases of pyogenic meningitis with a mean value of 78.22 and SD of 22.16 than among the cases of viral and tubercular meningitis. Lymphocytic predominance was observed in tubercular meningitis with mean of 75.5 and SD of 24.12 than viral and pyogenic meningitis. Both PMN and lymphocyte count had a clear statistical significance with 'p' value <0.001 in this study.

Conclusion: This present study concluded that CSF lactate could be a reliable and valid marker in early differentiation of pyogenic from cases of non-pyogenic meningitis. Early detection may help in early decision on the type and institution of appropriate management could reduce the mortality and morbidity of meningitis.

Keywords: Pyogenic Meningitis, Non-Pyogenic Meningitis, CSF lactate.

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 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]

Meningitis can be caused by various etiologies like tubercular, pyogenic and aseptic/viral. Meningitis is a major global health issue, particularly in developed countries. Among various types of meningitis, pyogenic/bacterial meningitis is one of the common infectious diseases of the CNS in India. Meningitis a critical disease associated with notable morbidity and mortality. [6] Moreover, long-term sequelae such as palsies, hearing loss and personality changes influence approximately 40% of survivors. P [7] The worldwide distribution of Pneumococcal, Haemophilus, and meningococcal meningitis has been observed and mainly in young age groups. Incidence of meningitis has substantially reduced in developed countries after the introduction of vaccines against these agents. But incidence remains the same in the developing world. The detection of a high level of CSF lactate has shown promising results in the diagnosis of bacterial/pyogenic meningitis. Validation of CSF lactate in clinical studies would complement clinical diagnosis and enhance the accuracy of diagnosis.

The aim of the present study was to determine the usefulness of CSF lactate as a diagnostic marker to differentiate pyogenic meningitis from non-pyogenic meningitis.

Materials and Methods

A hospital based one year prospective study was conducted in the Department of General Medicine (Emergency), IGIMS, Patna, Bihar, India for one year . Total of 50 cases of meningitis which were diagnosed upon clinical evaluation were included in the study. The study was conducted as per the guidelines of the committee. The study protocol was explained to all the participants and written informed consent was obtained from them. All the cases suspected with meningitis above 18 years of age irrespective of sex were admitted and clinically evaluated. Cases were examined for signs and symptoms of meningitis by a senior resident of the department and noted in a separate predesigned questionnaire sheet. The socio demographic data, history, age, gender, duration of signs and symptoms were recorded by interviewing the case or from the attendant of the case and noted in the questionnaire sheet. Neurological assessment of the cases for neck rigidity, kernig's sign or bridzinski's sign and any focal neurological inadequacy, cranial nerve palsies, hemiparesis and any signs of cerebral dysfunction which may include minor ailments like confusion, delirium or grave elements like diminishing level of sensorium and coma.

All the cases were clearly examined and appropriate haematological, radiological investigations were performed immediately upon admission. Patients with conditions which may cause elevated levels of lactate in CSF like brain hypoxia, seizures, brain trauma, recent CVA, subarachnoid haemorrhage and cases on immunosuppressive therapy, fungal meningitis and HIV were excluded from the study. Lumbar puncture was done under strict aseptic precautions and 10 ml of CSF collected and send to central laboratory for estimation of all biochemical parameters like sugars, protein, lactate, cell counts (Lymphocytes, neutrophils), Adenosine deaminase (ADA) levels. CSF lactate was estimated by enzymatic method using ABL 555 blood gas analyzer. The reference range in this study was 1.2-2.1mmol/L but ranges from 0.6-3.1mmol/L.4 The results of the CSF analysis were noted and based on findings the cases were grouped as,

- **Pyogenic meningitis:** Neutrophilic pleocytosis (10-10000 cells/mm3), protein >45mg/dl, sugar <40mg/dl.
- **Nonpyogenic:** Tubercular or Viral meningitis.
- **Tubercular**

Lymphocytic pleocytosis (10-1000cells/mm3). Protein >45mg/dl, sugars >2/3rd of blood sugar values, elevated ADA levels and demonstration of AFB on Zn staining.

Viral

Lymphocytic pleocytosis (25-500cells/mm3), slightly elevated protein (20-80mg/dl), normal sugars and ADA levels without bacteria on staining.

Statistical Analysis

Data were entered into the Microsoft Excel spreadsheet, and descriptive statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 20. Results on continuous measurements were presented as mean and standard deviation. Results on categorical measurements were presented as percentages. Significance was assessed at 5% level of significance. The chi‑square test was used to assess the significance of the study parameters on a

categorical scale between the groups.

Results

Table 1: Age, gender and type of meningitis distribution and CSF lactate levels

Age in years	**N%**
19-30	8 (16)
31-40	9 (18)
41-50	10 (20)
51-60	13 (26)
More than 60	10 (20)
Gender	
Male	30 (60)
Female	20 (40)
Type of meningitis	
Non-pyogenic	30 (60)
Tubercular	12
Viral	18
Pyogenic	20 (40)

Meningitis was common in the age group 51-60 (26%). Male patients (60%) were more than female patients (40%). Most number of cases was pyogenic meningitis (58%) while 42% were of non-pyogenic meningitis. Statistically CSF lactate levels were significantly increased in pyogenic meningitis cases when compared to CSF lactate levels in non-pyogenic meningitis patients.

Table 2: Signs and symptoms of cases in the study

Clinical signs and symptoms		**No**	**%**
	Fever	46	92
Symptoms	Headache	36	72
	Vomiting	37	74
	Altered sensorium	31	62
	Neck stiffness	32	64
	Kernig's sign	29	58
Signs	Brudzinski's sign	35	70
	Cranial nerve palsy	9	18

Fever was the most common symptom (92%) followed by vomiting (74%), headache (72%) and altered sensorium in 62% of cases. Brudzinski's sign was observed in 70% of cases and neck stiffness in 64%, kernig's sign in 58% and nerve palsies in 18% of cases.

Table 3: Analysis of cytological parameters of CSF among cases in the study

CSF parameters	**Type of Meningitis**	**Number of cases**	**Mean**	**SD**	**Range**	**p-value**
Total count	Tubercular	12	144.24	65.02	21-248	
	Viral	18	126.44	98.2	22-435	0.082
	Pyogenic	20	842.88	115.25	44-2687	
PMN	Tubercular	12	38.06	30.2	02- 98	
	Viral	18	34.46	18.22	04-78	<0.001
	Pyogenic	20	78.22	22.16	21-102	
Lymphocytes	Tubercular	12	75.5	24.12	11-114	
	Viral	18	68.12	19.11	34- 99	<0.001
	Pyogenic	20	28	11.26	5-78	

The mean total cell count was highest in cases of pyogenic meningitis with a mean of 842.88 and SD of 115.25 than viral and tubercular meningitis. However no statistical significance was associated with total count and types of meningitis. ('p' value -0.082) A clear neutrophil predominance was observed in all cases of pyogenic meningitis with a mean value of 78.22 and SD of 22.16 than among the cases of viral and tubercular meningitis. Lymphocytic predominance was observed in tubercular meningitis with mean of 75.5 and SD of 24.12 than viral and pyogenic meningitis. Both PMN and lymphocyte count had a clear statistical significance with 'p' value <0.001 in this study.

Table 4: Analysis of biochemical parameters of CSF among cases in the study

CSF parameters	Type of meningitis	Number of cases	Mean	SD	Range	p' value
Sugar(mg/dl)	Tubercular	12	48.22	12.48	22.1-42.15	
	Viral	18	73.17	16.24	41.2-124.24	0.003
	Pyogenic	20	42.1	22.48	10.24-142.1	
Protein(mg/dl)	Tubercular	12	195.25	212.24	47-279	
	Viral	18	96.22	44.26	72-240	0.022
	Pyogenic	20	272.1	144.26	78-847	
Lactate(mmol/l)	Tubercular	12	5.1	1.54	2.1-6.8	
	Viral	18	2.1	0.84	1-4.1	<0.001
	Pyogenic	20	12.58	3.57	3.1-15.8	
CSF sugar/Blood sugar ratio	Tubercular	12	0.0328	0.0726	0.24-0.48	
	Viral	18	0.072	0.1236	0.47-0.87	<0.001
	Pyogenic	20	0.2524	0.1216	0.076-0.048	

This study revealed that mean sugar levels are higher in viral (73.17±16.24) than pyogenic (42.1±22.48) and tubercular meningitis (48.22±12.48). Mean CSF protein was highest in pyogenic meningitis (272.1±144.26) than viral (96.22±44.26) and tubercular meningitis (195.25±212.24). In this study, no statistical significance was associated with sugar and protein levels in CSF and types of meningitis. CSF sugar to blood sugar ratio was <0.4 in both pyogenic meningitis and tubercular meningitis and >0.6 in viral meningitis.

Table 5: Analysis of CSF lactate (mmol/L) in different group of meningitis

Type of meningitis	Lactate		Total	p' value
	≤2.1	>2.1		
Tubercular	4	8	12	
Viral	8	10	18	<0.001
Pyogenic	0	20	20	
Total	12 (24%)	38 (76%)	50	

In this study, 12 cases of tubercular meningitis demonstrated elevated levels of CSF lactate with a cut-off value of >2.1 mmol/l, 10 cases of viral meningitis and all 20 cases of pyogenic meningitis (100%). A clear statistical significance was observed with regard to CSF lactate levels and types of meningitis in this study. This study revealed that of the total 50 cases, 38 cases (76%) had elevated levels of lactate (>2.1 mmol/L).

Discussion

Meningitis is serious and a life-threatening condition among any age group associated with serious mortality and morbidity. It is actually defined as acute inflammation of the protective membranes surrounding the brain and spinal cord known as meninges. The cause may be bacterial, viral and also fungal with different set of morbidity and severity. Differentiating bacterial from viral by clinical signs and symptoms is quite challenging to the clinicians. Bacterial meningitis is associated with severe mortality and post sequelae than viral and fungal meningitis. Prompt diagnosis and appropriate antibiotic therapy are required to reduce the mortality and morbidity. Any delay in diagnosis and appropriate therapy will worsen the prognosis. Hence early and rapid differentiation between bacterial and viral meningitis is essential in early initiation of therapy. [8] In recent years various studies have shown CSF lactate may be a good marker to differentiate bacterial from other cause of meningitis. Few studies have differed saying that CSF lactate offers no additional information over other markers like CRP and procalcitonin. The above variables are never used as routine in diagnosis or differentiation of bacterial from viral meningitis. [1] 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. [9,10]

Meningitis was common in the age group 51-60 (26%). Male patients (60%) were more than female patients (40%). Similar findings were reported in the study of van de Beek et al, with 75% of males and 25% females. [11] Mean age of the male was higher than the female in this study which is similar to many studies universally, but the noted feature of the study was mean age of all the cases was 38.12±11.2 years which was less than many studies conducted in the west and few studies in India. [12,13] Most number of cases was pyogenic meningitis (58%) while 42% were of non-pyogenic

meningitis. Statistically CSF lactate levels were significantly increased in pyogenic meningitis cases when compared to CSF lactate levels in non-pyogenic meningitis patients. Fever was the most common symptom (92%) followed by vomiting (74%), headache (72%) and altered sensorium in 62% of cases. Brudzinski's sign was observed in 70% of cases and neck stiffness in 64%, kernig's sign in 58% and nerve palsies in 18% of cases. Few studies in the west reported higher incidence of nerve palsies with 30-40% in their studies but this is quite variable depending upon the associated co-morbidities and age selection of cases in the study. [14]

The mean total cell count was highest in cases of pyogenic meningitis with a mean of 842.88 and SD of 115.25 than viral and tubercular meningitis which is similarly reported in the study of Ranbeer Kumar Singh et al. Pyogenic meningitis showed neutrophil (PMN) predominance whereas non-pyogenic group showed lymphocyte predominance which was similar to findings of Ranbeer Kumar Singh et al, and was associated with significant statistical association in this study. [15] However, Negrini et al, have reported that most of the patients with aseptic meningitis had neutrophil predominant pleocytosis. [16] However, no statistical significance was associated with total count and types of meningitis. ('p' value -0.082) A clear neutrophil predominance was observed in all cases of pyogenic meningitis with a mean value of 78.22 and SD of 22.16 than among the cases of viral and tubercular meningitis. Lymphocytic predominance was observed in tubercular meningitis with mean of 75.5 and SD of 24.12 than viral and pyogenic meningitis. Both PMN and lymphocyte count had a clear statistical significance with 'p' value <0.001 in this study. This study revealed that mean sugar levels are higher in viral (73.17±16.24) than pyogenic (42.1 ±22.48) and tubercular meningitis (48.22±12.48). Similar findings were reported in the study of Huy et al, who reported that mean sugar levels in viral meningitis was 78.01±12.41 and mean CSF protein was 285.1±122.28 in his study and was statistically significant. [17] CSF sugar to blood sugar ratio was <0.4 in both pyogenic meningitis and tubercular meningitis and >0.6 in viral meningitis and the ratio of CSF sugar to blood sugar is a better parameter in this study which was similar to the findings of Viallon A et al. [18]

Mean CSF protein was highest in pyogenic meningitis (272.1±144.26) than viral (96.22±44.26) and tubercular meningitis (195.25±212.24). In this study, no statistical significance was associated with sugar and protein levels in CSF and types of meningitis. CSF sugar to blood sugar ratio was <0.4 in both pyogenic meningitis and tubercular meningitis and >0.6 in viral meningitis. In this study, 12 cases of tubercular meningitis demonstrated elevated levels of CSF lactate with a cut-off value of >2.1 mmol/l, 10 cases of viral meningitis and all 20 cases of pyogenic meningitis (100%). A clear statistical significance was observed with regard to CSF lactate levels and types of meningitis in this study. This study revealed that of the total 50 cases, 38 cases (76%) had elevated levels of lactate (>2.1 mmol/L). In the present study, CSF lactate was high in all cases of pyogenic meningitis. The further evaluation suggests that there was no correlation between mean CSF lactate value and gram stain/culture results. Donald P et al [19] have reported that CSF lactate does not hold marked advantages over conventional chemical analysis of CSF in differentiating Tubercular meningitis from aseptic meningitis. 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. [20] 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). [21]

Conclusion

This present study concluded that CSF lactate could be a reliable and valid marker in early differentiation of pyogenic from cases of non-pyogenic meningitis. Early detection may help in early decision on the type and institution of appropriate management could reduce the mortality and morbidity of meningitis. Associated with CSF blood/CSF sugar ratio is also a helpful and supportive marker in differentiating viral, tubercular and pyogenic meningitis.

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