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Estimation of CSF lactate as a diagnostic marker to differentiate pyogenic meningitis from nonpyogenic meningitis

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ABSTRACT

Introduction: Meningitis is a serious clinical problem in many regions of the world especially in the developing countries. Early diagnosis and appropriate treatment of the type of meningitis is crucial to reduce associated mortality and morbidity. The role of CSF lactate in the differential diagnosis between pyogenic from nonpyogenic meningitis has been debatable for long. We investigated the diagnostic value of CSF lactate in meningitis patients for discriminating between pyogenic and nonpyogenic meningitis in our institute for two years.

Materials and Methods: A cross-sectional study was done in 40 cases of suspected meningitis of varied etiologies from October 2011 to October 2013. CSF samples were taken immediately on admission. Based on CSF cytology and biochemical parameters and other specific assays, patients were divided into pyogenic, tubercular and aseptic/viral meningitis. CSF lactate was estimated by the ISE (Ion-selective electrode) method.

Results: Of the 40 patients with meningitis, 16 were pyogenic and 24 nonpyogenic (9 tubercular and 15 aseptic/viral). Mean CSF lactate levels was 11.66 mmol /L, 4.0 mmol /L and 1.99 mmol /L in pyogenic meningitis, tubercular meningitis and viral meningitis respectively ($P<0.001$). Mean CSF lactate was significantly high in pyogenic meningitis and tubercular meningitis compared to viral meningitis. Using a higher cut off value of 5 mmol/L, CSF lactate helped in differentiating pyogenic from tubercular meningitis ($P<0.001$).

Conclusion: CSF lactate can provide legitimate, quick and explicit diagnostic information in differentiating pyogenic from nonpyogenic meningitis (tubercular and viral).

1. Introduction

Inflammation of the membranes of meninges characterizes Meningitis - clinical syndrome that encloses the brain and spinal cord. These layers of meninges consist of the following: 1. Dura mater - A tough and outermost membrane 2. Arachnoid mater- A web-like middle membrane 3. Pia mater- the innermost layer which adheres closely to the brain. Subarachnoid space lies between arachnoid and pia mater and contains many of the blood vessels that feed the brain and spinal cord.[1] 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.[2] Moreover, long-term sequelae such as palsies, hearing loss and personality changes influence approximately 40% of survivors.[3] 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. For identifying the cause of meningitis, clinical features, routine CSF parameters, and radiological findings are often inadequate. In developing

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countries, Gram's stain and AFB stain of CSF are the most common rapid methods of detection of the organism, however, these methods lack sensitivity. Another common method used for diagnosis is the culture of CSF but it is time-consuming. Although PCR and nowadays Real-time-PCR are extremely sensitive and specific tests for diagnosis, however being expensive and less available these methods cannot be used for the routine purpose. Therefore, a robust cost-effective test should be available for differentiation among various types of meningitis. 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 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.

We have undertaken this study with the main purpose of evaluating the efficacy of CSF lactate in differentiating pyogenic/ bacterial from nonpyogenic meningitis.

2. Materials and Methods

2.1. *Patients and setting*

A hospital-based cross-sectional study of all clinically suspected cases (40 cases) of meningitis of different age groups (18 years or more) admitted to M.S.Ramaiah hospitals from October 2011 to October 2013 was done. Conditions which can be responsible for the elevation of CSF lactate such as brain hypoxia, recent stroke, brain trauma, subarachnoid hemorrhage and seizures, Patients with fungal meningitis and HIV and Immunosuppressive therapy were excluded in the investigation. The sample size was estimated based on hypothesis testing for two means and evidence obtained from a study done by Ali Hassan Abro et al on CSF lactate level as a diagnostic tool to differentiate acute bacterial from viral meningitis, at Infectious disease dept., Rashid Hospital Dubai.[5]

Considering the SD in 1st group as 6.1, 2nd group as 0.6, mean difference as 3, effect size 0.8955, alpha error 5% and power of test at 80% for a 2 sided test, the estimated sample size was 33, which was rounded off to 40 subjects. Data was aggregated by pretested semi-structured questionnaire, clinical-diagnosis, and investigations. The diagnosis of meningitis was made on the basis of clinical symptoms and signs like headache, nausea, vomiting, fever, neck rigidity, presence of kernig's sign and or brudzinski's sign, altered sensorium, any focal neurological inadequacy, cranial nerves palsies, hemiparesis, seizures and or signs of cerebral dysfunction ranging from confusion, delirium, diminishing level of sensorium from lethargy to coma. Lumbar puncture was conducted on the patients instantly on admission. The assay used in the study was based on the enzymatic method by using Lactate Electrode using ABL 555 Blood gas analyzer (Radiometer Copenhagen, Denmark).

2.2. *CSF analysis*

CSF lactate analysis was performed for all cases with abnormal CSF cytochemical pictures. All routine and other relevant investigations were recorded from case files. The types of meningitis were categorized on the following basis: Pyogenic meningitis: CSF exhibiting neutrophilic pleocytosis (10-10000cells/mm3), elevated protein (>45mg/dl), low sugars (<40 mg/dl) with or without bacteria displayed on Gram stain/culture. Nonpyogenic meningitis: a. Tubercular meningitis: CSF exhibiting lymphocytic pleocytosis (10-1000cells/mm3), elevated protein (>45mg/dl), low sugars (<2/3rd blood sugar) with high CSF ADA levels (at a higher level to the ref range of lab) with or without bacteria demonstrated on ZN staining/culture/PCR. b. Viral meningitis: CSF exhibiting lymphocytic pleocytosis (25-500cells/mm3), normal/slightly elevated protein (20-80mg/dl), normal sugars with absent/normal CSF ADA levels and negative for bacteria on microscopy/cultures/PCR. The normal reference range considered for study was 1.2 to 2.1 mmol/L as standardized by the University of Colorado hospital laboratories approved by the college of American pathologists (updated on June 1, 2011).

2.3. *Statistical analysis*

Statistical analyses of the data were conducted using the software IBM SPSS 17.0 version. The frequency distribution (mean), Independent t-test, S.D. with 95% confidence limit and correlation statistics were the statistical parameters utilized to analyze the data.

3. Results

3.1. *Demographic data*

Out of 40 cases of meningitis considered for investigation, 16 were pyogenic and 24 non-pyogenic (9 tubercular and 15 viral)Figure 1. In our study, almost equal sex distribution was undertaken with 52.5% being males and 47.5% females Figure 2. shows the type of the age group present in the study; most cases were of 18-29 (32.5%) and 40-49(25%) age groups.

3.2. *Clinical presentation*

In the present investigation, fever (80%) was most common symptom followed by headache (77.5%), altered sensorium (60%) and vomiting (40%) Figure 4 . Signs of meningeal irritation were present in 72.5% of cases. Abducent nerve palsy was seen in 2 cases (5%).

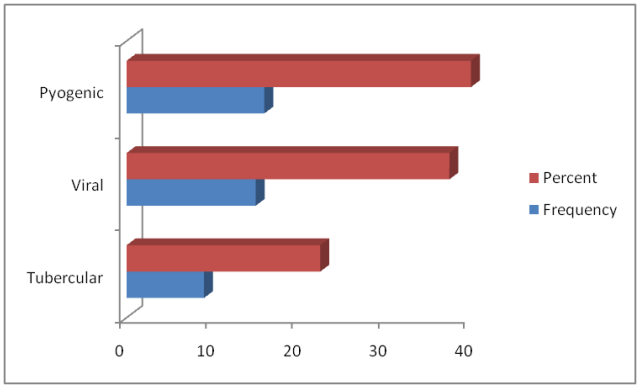

Fig. 1: Frequency of different groups of meningitis

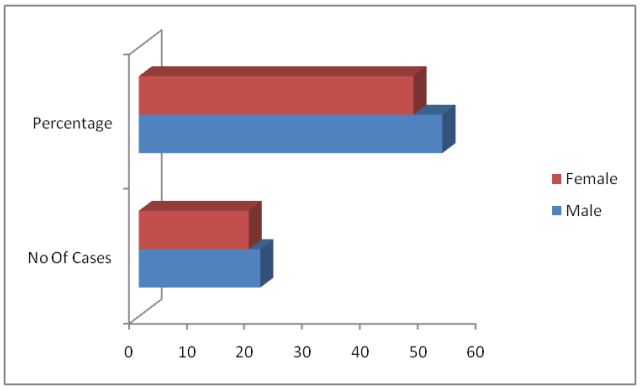

Fig. 2: Sex wise distribution of cases

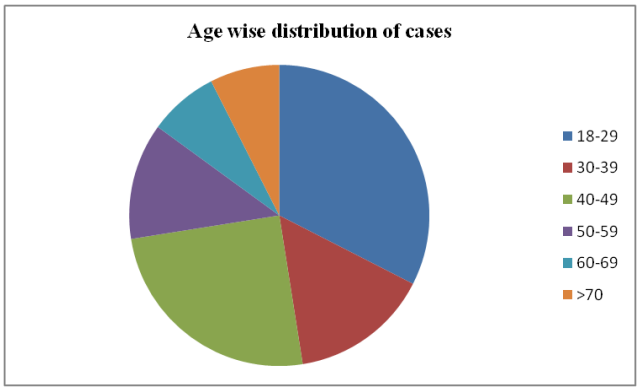

Fig. 3: Age wise distribution of cases

The mean CSF total cell count was higher (with neutrophil predominance) in pyogenic meningitis group compared to nonpyogenic meningitis group in the current study.Table 1

Our study reveals that the mean CSF sugar was low in pyogenic and tubercular meningitis compared to viral meningitis.CSF sugar to blood sugar ratio was <0.4 in both pyogenic meningitis and tubercular meningitis and >0.6 in viral meningitis. Mean CSF protein was highest in pyogenic

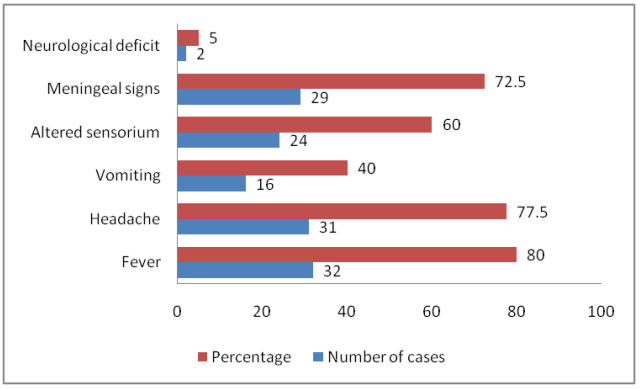

Fig. 4: Analysis of clinical symptoms and signs

meningitis (267.78 mg/dl) followed by tubercular (184.99 mg/dl) and viral (96.01mg/dl). Mean CSF lactate was high in both pyogenic and tubercular meningitis compared to viral meningitis. However mean CSF lactate was very high (11.66 mmol /L) in pyogenic group compared to tubercular (4.0 mmol/L)Table 2 .

We found that the mean total leucocyte count (TLC) and mean absolute neutrophil count (ANC) was high in pyogenic group compared to nonpyogenic group. Mean serum procalcitonin (PCT) was high in pyogenic group and normal in nonpyogenic group Table 3 .

Mean CSF lactate was high in both pyogenic meningitis and tubercular meningitis compared to viral meningitisTables 4, 5 and 6 .

Using a higher cut off value of 5 mmol/L, CSF lactate was useful in differentiating pyogenic meningitis from tubercular meningitis with statistical significance Table 7 .

The data obtained in the present study revealed that CSF lactate was directly correlating with serum procalcitonin level in pyogenic meningitis group Table 8 .

Our study reveals that CSF lactate level was directly correlating with CSF sugar to blood sugar ratio in pyogenic meningitis group Table 9 .

4. Discussion

In the case of acute meningitis, the accurate initial diagnosis is the cornerstone in therapeutic decision making. Pyogenic meningitis is associated with significant morbidity and mortality and is a common and serious life-threatening disease.[6] To differentiate between bacterial and viral meningitis, clinical signs have been manifested to have sensitivity and specificity within a range and are of less significance for differentiating among the types of meningitis6. In only 60-80% cases, direct CSF examination on an emergency basis provides evidence of bacterial meningitis.[7] In our study, only 2 out of 16 cases of pyogenic meningitis had positive gram stain and only one case was culture-positive which clearly shows that the CSF

Table 1: Analysis of CSF cytological parameters in different group of meningitis

CSF parameters		N	Mean	SD	Min.	Max.	'F' value	'p' value
	Tubercular	9	103.00	89.01	10	264		
TC(cells/mm3)	Viral	15	133.47	119.94	27	450	3.0	0.058
	Pyogenic	16	727.06	1181.10	28	3690		
	Tubercular	9	29.11	31.970	0	90		
PMN	Viral	15	27.80	20.67	2	70	22.9	<0.001
	Pyogenic	16	78.00	18.18	25	98		
	Tubercular	9	70.89	31.97	10	100		
Lymphocyte	Viral	15	68.87	23.20	30	98	19.5	<0.001
	Pyogenic	16	22.00	18.18	2	75		

Table 2: Analysis of CSF biochemical parameters in different group of meningitis

CSF parameters		N	Mean	SD	Min.	Max.	'F' value	'p' value
	Tubercular	9	44.31	16.33	23.4	69.0		
Sugar(mg/dl)	Viral	15	67.72	16.65	45.7	112.0	6.24	0.005
	Pyogenic	16	41.31	28.22	8.4	123.0		
	Tubercular	9	131.8	33.79	84	180		
RBS(mg/dl)	Viral	15	114.6	30.72	86	201	1.66	0.203
	Pyogenic	16	172.6	136.4	73	560		
	Tubercular	9	.3278	.0719	.20	.40		
CSF sugar/blood sugar Ratio	Viral	15	.6066	.1144	.44	.86	49.1	<0.001
	Pyogenic	16	.2524	.1047	.08	.40		
	Tubercular	9	184.9	209.9	48	723		
Protein(mg/dl)	Viral	15	96.01	42.93	66	206	3.43	0.043
	Pyogenic	16	266.7	236.1	68	895		
	Tubercular	9	4.000	1.280	2.0	6.3		
Lactate(mmol/L)	Viral	15	1.993	.6923	1.0	3.7	80.9	<0.001
	Pyogenic	16	11.66	3.264	2.9	15.6		

Table 3: Analysis of various blood parameters in different group of meningitis

Blood parameters		N	Mean	SD	Min.	Max.	'F' value	'p' value
	Tubercular	9	8728.89	2216.4	5000	13060		
TLC(cells/mm3)	Viral	15	7816.00	2521.7	3790	11870	10.33	<0.001
	Pyogenic	16	13939.3	5504.9	6600	23670		
	Tubercular	9	5933.89	2348.6	1950	10186		
ANC(cells/mm3)	Viral	15	5671.20	2042.9	2609	9027	8.132	0.001
	Pyogenic	16	10431.2	4986.0	3690	17924		
	Tubercular	9	24.11	15.775	8	48		
ESR	Viral	15	19.67	21.744	6	81	0.450	0.641
	Pyogenic	16	27.75	28.539	5	109		
	Tubercular	9	.203	.1714	.02	.5		
Ser. PCT(ng/dl)	Viral	15	.240	.2828	.04	1.1	4.043	0.026
	Pyogenic	16	4.813	7.8437	.20	27.2		

Table 4: Analysis of CSF lactate(mmol/L) in different group of meningitis

	Lactate		Total	'F' 2 value	'p' value
	<=2.1	>2.1			
Tubercular	1	8	9		
Viral	13	2	15		
Pyogenic	0	16	16	28.474	<0.001
Total	14	26	40		
	35.0%	65.0%	100.0%		

Table 5: Comparison of CSF lactate between viral meningitis and pyogenic meningitis.

	CSF Lactate		**Total**	**P value**
	<=2.1	**>2.1**		
Viral	13	2	15	<.001
Pyogenic	0	16	16	
Total	13	18	31	
	41.9%	58.1%	100.0%	

Table 6: Comparison of CSF lactate between viral meningitis and tubercular meningitis

	CSF Lactate		**Total**	**P value**
	<=2.1	>2.1		
Tubercular	1	8	9	<.001
Viral	13	2	15	
Total	14	10	24	
	58.3%	41.7%	100.0%	

Table 7: Comparison of CSF lactate between pyogenic meningitis and tubercular meningitis using a cut off value of 5 mmol/L.

	CSF Lactate		**Total**	**P value**
	<=5.0	>5.0		
Tubercular	8	1	9	<.001
Pyogenic	1	15	16	
Total	9	16	25	

Table 8: CSF lactate in relation to serum procalcitonin (PCT) in pyogenic meningitis

Group	**CSF lactate**	**Ser. PCT**		**Total**
		<=0.5	>0.5	
Pyogenic	<2.1	0	0	0
	>2.1	4	12	16
		25%	75%	100.0%

Table 9: CSF lactate in relation to CSF glucose/blood glucose ratio pyogenic meningitis

Group	**Ratio**	**Lactate**		**Total**
		<=2.1	>2.1	
Pyogenic	<=0.4		16	16
			100.0%	100.0%
	Total		16	16
			100.0%	100.0%

Table 10: Analysis of prognosis in different groups of meningitis

Group	**Outcome**		**Total**
	Improved	**Expired**	
Tubercular	7	2	9
	77.8%	22.2%	100.0%
Viral	14	1	15
	93.3%	6.7%	100.0%
Pyogenic	13	3	16
	81.3%	18.8%	100.0%
Total	34	6	40
	85.0%	15.0%	100.0%

cytochemical parameters play a key role in the diagnosis of the type of meningitis. In our study, there was almost equal sex distribution with 52.5% being males and 47.5% being females while in Ali Hassan Abro et al study, the mean age of the patients was 33.73 ± 11.7 years where Males (86.5%) outnumbered the females (13.43%) in the study.[5] In Viallon et al study mean age group was 55 ± 20 years and 35 ± 18 years in bacterial meningitis and viral meningitis respectively. In our study,[8] the most common symptom of meningitis was fever (80%), followed by headache (77.5%), altered sensorium (60%) and vomiting (40%). Signs of meningeal irritation were present in 72.5% of cases. This suggests that the classical clinical triad of fever, headache and neck stiffness is not consistently seen in all the cases. Neurologic deficits in the form of abducent nerve palsy were seen in 5% of cases. However, the incidence of neuro deficits may be underestimated in this study as major deficits like hemiplegia constituted exclusion criteria. In Khatua et al study, neck rigidity was noted in 54 % of cases and kernig's sign in 40% of cases.[9] In studies done by Van de Beek et al and Virmani et al cranial nerve palsy were seen in 33% and 27% cases respectively.[10,11] The present study revealed that the mean CSF total cell count (TC) was higher in the pyogenic group compared to the non-pyogenic group i.e, tubercular and viral meningitis. Pyogenic meningitis showed neutrophil (PMN) predominance where a non-pyogenic group showed lymphocyte predominance. Baker RC et al and Viallon et al have found similar findings in their study with high CSF pleocytosis with neutrophil predominance in bacterial meningitis compared to viral meningitis.[8,12] However, Negrini et al have reported that most of the patients with aseptic meningitis had neutrophil predominant pleocytosis in CSF.[13] In our study CSF differential leucocyte count helped differentiate pyogenic from nonpyogenic meningitis with statistical significance. In the present findings, mean CSF sugar was low in pyogenic (41.31mg/dl) and tubercular meningitis (44.31mg/dl) compared to viral meningitis (67.72mg/dl). A study done by Ali Hassan Abro et al reported similar findings with mean CSF sugar 26.5 ± 21.6 and 67 ± 18.96 mg/dl in bacterial and viral meningitis respectively8. CSF sugar to blood sugar ratio was <0.4 in both pyogenic meningitis and tubercular meningitis and >0.6 in viral meningitis. Spanos et al and Viallon et al also noted similar findings in their study.[8,14] Because CSF sugar varies with blood sugar, the ratio of CSF sugar to blood sugar is a better parameter.

Mean CSF protein was found to be highest in pyogenic meningitis (267.78 mg/dl) followed by tubercular meningitis (184.99 mg/dl) and viral meningitis (96.01mg/dl). Similar findings noted in studies done by Viallon et al with mean CSF protein 4.9±4.6 g/L in bacterial meningitis versus 1±0.6 g/L in viral meningitis9. Ray P et al also noted similar findings in their study.[15] Robert L et al in their study could not find CSF lactate a better marker compared to other biochemical parameters like sugar, protein, cell count and typing.[16] In our study mean CSF lactate was high in both pyogenic and tubercular meningitis compared to viral meningitis with statistical significance (p <.001). However, mean CSF lactate was very high (11.66 mmol /L) in pyogenic meningitis compared to tubercular (4.0 mmol /L). In a study done by Ali Hassan Abro et al, mean CSF lactate was 14.96±6.13 mmol /L and 2.38±0.59 mmol /L in bacterial meningitis and viral meningitis respectively. Smith et al and Genton B et al also have noted similar findings in their study.[17,18] Viallon et al also noted similar findings with mean CSF lactate of 9±5 mmol /L in bacterial meningitis and 2.6±1.6 mmol /L in viral meningitis and this study was done in patients with negative direct examination of CSF for bacteria.[8] In the present study, CSF lactate was high in all cases of pyogenic meningitis. The further evaluation suggests that there is no correlation between mean CSF lactate value and gram stain/culture results. Donald P et al have reported that CSF lactate does not hold marked advantages over conventional chemical analysis of CSF in differentiating Tubercular meningitis from aseptic meningitis.[19] But in our study mean CSF lactate was able to differentiate Tubercular meningitis (4 mmol /L) from viral/aseptic meningitis (1.99 mmol /L) (p <0.001). Tang LM et al also noted higher CSF lactate in tubercular meningitis (3.9 mmol/L).[20] In the present investigation using a higher cut off value of 5 mmol /L, CSF lactate helped in differentiating pyogenic meningitis from tubercular meningitis (p-value <0.001). In the present study, mean blood total leucocyte count (TLC) and mean absolute neutrophil count (ANC) were high in the pyogenic meningitis group compared to the non-pyogenic meningitis group. Ali Hassan Abro et al noted similar findings in their study. Also, in our study, mean serum procalcitonin (PCT) was high (4.83ng/ml) in the pyogenic meningitis group compared to the non-pyogenic meningitis group. In the study reported by Schwartz et al[10] among 16 patients with bacterial meningitis had serum PCT >0.5ng/ml. In our study 13 out of 16 patients with pyogenic meningitis had serum PCT >0.5. Jereb et al and viallon et al also noted similar findings in their study.[8,21] The mean CSF lactate level (11.66 mmol /L) value obtained in our investigation directly correlated with mean serum procalcitonin level (4.83ng/ml) in the pyogenic meningitis group. All 16 bacterial meningitis patients had high CSF lactate levels and 13 out 16 patients had high serum PCT level which is supported by a similar correlation noted in Viallon et al study.[8] Also, our study reveals the direct correlation of the mean CSF lactate level (11.66mmol/L) value with mean CSF sugar to blood sugar ratio (0.25) in the pyogenic meningitis group. A similar correlation was noted by Viallon et al in their study9. CSF lactate

was found to be higher in those expired compared to those who survived in both pyogenic meningitis and tubercular meningitis group. Similar findings were noted by Ali Hassan Abro et al in pyogenic meningitis group in their study8. Thus the magnitude of CSF lactate level may help in predicting poor outcome and determine likely prognosis.

5. Conclusion

CSF lactate level is a rapid, relatively economical and modest procedure that can be of great value as a diagnostic marker in the early differentiation of pyogenic meningitis and tubercular meningitis from viral meningitis, helping in the early institution of appropriate treatment and decreasing mortality and complications.

In our study, the CSF lactate level was significantly higher in pyogenic meningitis and tubercular meningitis group compared to viral meningitis. With a cut off value of 2.1 mmol/L, CSF lactate value was useful in differentiating both pyogenic and tubercular meningitis from viral/aseptic meningitis. Also, with a cut off value of 5.0 mmol/L, CSF lactate was useful in differentiating pyogenic meningitis from tubercular meningitis. CSF lactate value directly correlates with serum procalcitonin level and CSF sugar/blood sugar ratio.

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7. Source of Funding

None.

8. Conflict of Interest

None.

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