

## Original Research Article

# Estimation of cerebrospinal fluid lactate level to differentiate between pyogenic and non-pyogenic meningitis: a prospective analytical study

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## ABSTRACT

**Background:** Meningitis is one of the common causes of serious morbidity and mortality and is one of the common causes of intensive care unit (ICU) admissions. The meningitis can be broadly divided into bacterial, viral or fungal meningitis. It is important to differentiate between pyogenic and non-pyogenic meningitis because of obvious management implications. Cerebrospinal fluid (CSF) lactate levels can be used for differentiating pyogenic and non-pyogenic (viral/tubercular) meningitis.

**Methods:** This was a prospective analytical study in which cases diagnosed to be having meningitis were included on the basis of a predefined inclusion and exclusion criteria. Demographic details such as age, gender and socioeconomic status was noted in all the cases. A detailed clinical history was taken and a thorough clinical examination was done. Imaging (computerized tomography) was done in selected cases. CSF cytology, biochemistry and culture sensitivity were done in all cases. CSF lactate was determined in all cases.

**Results:** The CSF cytological examination showed that the mean total cell count was more ( $643.23 \pm 102.02$ ) in pyogenic meningitis as compared to non-pyogenic (viral/tubercular) meningitis ( $121.76 \pm 59.74$ ) and the difference was found to be statistically highly significant ( $p < 0.0001$ ). The analysis of CSF lactate levels showed that pyogenic meningitis cases had a significantly high level of CSF lactate as compared to non-pyogenic meningitis cases and the difference was found to be statistically highly significant ( $p < 0.0001$ ).

**Conclusions:** CSF lactate level is a good indicator in differentiating pyogenic and non-pyogenic meningitis.

**Keywords:** Meningitis, Pyogenic, CSF analysis, Lactate levels

## INTRODUCTION

Meningitis is one of the common causes of serious morbidity and mortality in developing as well as developed countries and remains one of the important pathologies for which intensive care is warranted. In simple words meningitis can be defined as inflammation of meninges.<sup>1</sup> The list of etiologies which can cause meningitis is exhaustive but can be broadly divided into bacterial or viral meningitis. In developing countries of

South East Asia tubercular meningitis remains one of the important causes of meningitis. The common predisposing factors for meningitis include extremes of age (neonates and old individuals), those with chronic medical conditions (chronic renal failure and uncontrolled diabetes), unimmunized children (influenza), immunocompromised persons (those having HIV/AIDS, on long term steroid or chemotherapeutic drugs), those with congenital heart disease, and intravenous drug abusers.<sup>2</sup>

In bacterial meningitis common offending organisms include *Streptococcus pneumoniae*, group B *Streptococcus*, *Neisseria meningitidis*, *Hemophilus influenzae* and *Listeria monocytogenes*.<sup>3</sup> On the other hand, viral meningitis is usually caused by viruses such as enteroviruses, mumps, Epstein Barr virus, herpes simplex virus, and varicella-zoster virus, measles and influenza viruses. Tubercular meningitis remains one of the important causes of meningitis in south east Asian countries including India and must be included in differential diagnosis of any patient presenting with features suggestive of meningitis.<sup>4</sup> Fungal infection is one of the less common causes of meningitis and is usually seen in patients who are generally immunocompromised such as those having acquired immunodeficiency syndrome (AIDS), those on long term steroids or patients undergoing chemotherapy for various malignancies or uncontrolled diabetics. Fungal meningitis is usually caused by *Cryptococcus neoformans*, *Aspergillus* and *Candida*.<sup>5</sup>

Irrespective of etiology the common clinical presentation of meningitis include nausea, vomiting, altered sensorium, headache, confusion, delirium, seizures and in severe cases coma. Patients at extremes of age (neonate and old individuals) may present with atypical presentations particularly in neonates a high index of suspicion is essential as the only sign a neonate with meningitis may present with can be refusal to feed. Delay in administration of appropriate antibiotics in these neonates may have devastating consequences including neonatal death.<sup>6</sup>

The diagnosis of meningitis depends upon complete blood count (leukocytosis in bacterial meningitis), imaging (computed tomography and magnetic resonance imaging) and cerebrospinal fluid (CSF) analysis. CSF analysis remains the gold standard test and the diagnosis of meningitis can only be confirmed by analyzing CSF. CSF analysis by biochemical (sugar, protein and lactate) cytological (neutrophils, lymphocytes and pus cells) markers and microbiological tests such as gram (gm) and Ziehl Neelsen (Zn) staining as well as culture sensitivity, can usually give a fair idea about etiological diagnosis.<sup>7</sup> CSF lactate level has been shown to be having a fairly good sensitivity for differentiating between pyogenic and non-pyogenic meningitis particularly if the other causes of raised CSF lactate levels such as intracranial hemorrhage, hypoxic encephalopathy and status epilepticus has been ruled out. This differentiation is important from management point of view. Hence CSF lactate level can be used by clinicians to differentiate between bacterial and non-bacterial meningitis.<sup>8</sup>

We conducted this study to evaluate the efficiency of CSF lactate level in differentiating pyogenic and non-pyogenic meningitis.

## METHODS

This was a prospective analytical study conducted in the department of general medicine, after approval of

institutional ethical committee, of a tertiary care medical college situated in an urban area. All patients admitted under department of medicine and diagnosed to be having meningitis were included in this study on the basis of a predefined inclusion and exclusion criteria.

Demographic details such as age, gender and socioeconomic status was noted in all the cases. The detailed history was taken particularly about history of fever, headache, vomiting and convulsions. Family history such as history of contact with tuberculosis patients was specifically asked for. Factors which may predispose an individual for development of meningitis such as history of medications (steroids and immunosuppressants), chronic diseases (renal failure, uncontrolled diabetes and HIV/AIDS) was asked for and if present was noted down. A detailed clinical examination was done for presence of predisposing factors. A thorough neurological examination was done to look for any focal neurological deficit, cranial nerve palsy or neck rigidity. Kernig's sign or Brudzinski's sign was Brudzinski's looked for and noted. Higher functions like orientation in time, place and person was determined. Presence of confusion, altered sensorium or delirium was also noted. A complete blood count was done in all the cases. Serum electrolytes, renal function tests and hepatic function tests were also done. Imaging (computerized tomography) was done in selected cases. A lumbar puncture was done after taking consent either from the patient or the caretaker (in cases who had altered sensorium) and cerebrospinal fluid analysis was done for CSF sugar, protein and lactate, CSF cytology was done (neutrophil, lymphocytes and presence of pus cells). Gm staining, acid fast bacilli (AFB) staining and CSF culture was done in all the cases. Depending upon the CSF biochemistry and cytology the cases were divided into pyogenic, mycobacterial and viral meningitis.

**Table 1: Criteria for diagnosis of bacterial, viral and tubercular meningitis.**

Diagnosis	Cytology	Biochemistry
<b>Bacterial meningitis</b>	Neutrophils more than 100/cu mm	Protein >45 mg/dl and sugar <40 mg/dl
<b>Viral meningitis</b>	Lymphocytic predominance (>100/cu mm)	Protein <45 mg/dl and sugar >40 mg/dl
<b>Tubercular meningitis</b>	Lymphocytic pleocytosis (100 cells/cu mm)	Protein >45 mg/dl, sugars >2/3rd of blood sugar values

CSF lactate level was determined in all the cases and a cut off level of 3.8 was considered for differentiation of bacterial and non-bacterial meningitis. The results of CSF lactate were compared with cytological and biochemical analysis of CSF. The statistical analysis was done using statistical package for the social sciences (SSPS) 21.0 software. P value less than 0.05 was taken as statistically significant.

**Inclusion criteria**

Patients with clinical diagnosis of meningitis and CSF analysis showing cytology and biochemistry suggestive of bacterial meningitis and/or CSF gm staining/culture showing presence of pyogenic organisms.

Patients with clinical diagnosis of viral meningitis and CSF analysis showing pleocytosis of 100 WBC with lymphocytic pleocytosis and CSF and blood culture negative for bacteria.

Patients with clinical diagnosis of tubercular meningitis and showing pleocytosis of 100 white blood cells (WBC) with lymphocytic pleocytosis and protein >45 mg/dl, sugars >2/3rd of blood sugar values.

**Exclusion criteria**

Cases in whom consent was refused by patient or caretaker.

Patients who received antimicrobial treatment before admission.

Patients in whom lumbar puncture is contraindicated such as those having thrombocytopenia, increased clotting time and lumbar puncture site infections or in those having raised intracranial tension.

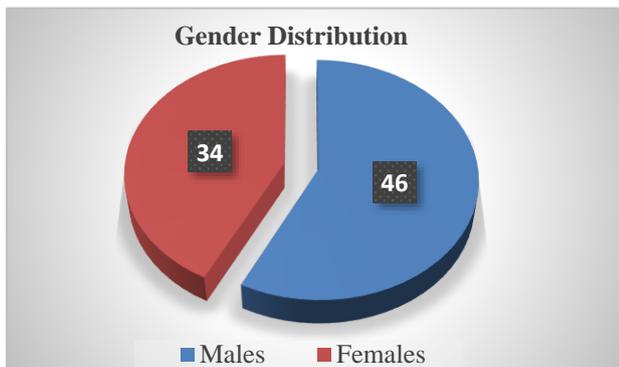
Patients with fungal meningitis.

Patients with serious co-morbidities such as malignancies, AIDS, and renal failure.

Conditions which are known to alter of CSF lactate levels such as stroke, hypoxia encephalopathy, head injury and status epilepticus.

**RESULTS**

A total of 80 patients were included in this study on the basis of a predefined inclusion and exclusion criteria. Out of total 80 patients there 46 (57.50%) males and 34 (42.50%) females with a male:female ratio of 1:0.739.



**Figure 1: Gender distribution of the studied cases.**

The analysis of age distribution of the studied cases showed that the most common age group in studied cases was found to be 31-40 years (66.67%) followed by 20-30 (16.67%) years and more than 40 years (13.33%). Only 1 patient (3.33%) was found to be in age group of less than 20 years (Table 2).

**Table 2: Age distribution of the studied cases.**

Age (years)	No. of patients	Percentage (%)
< 20	1	1.25
20-30	11	13.75
31-40	36	45.00
41-50	20	25.00
>50	12	15.00
<b>Total</b>	<b>80</b>	<b>100</b>

The mean age of the male patients was found to be 34.42±8.12 years while mean age of female patients was found to be 33.46±8.28 years. On statistical analysis the difference in mean age of male and female patients was found to be statistically not significant (Table 3).

**Table 3: Mean age in male and female patients.**

Sex	Mean age	P value
<b>Males</b>	38.42±7.12	p=0.53
<b>Females</b>	37.46±6.28	Not significant

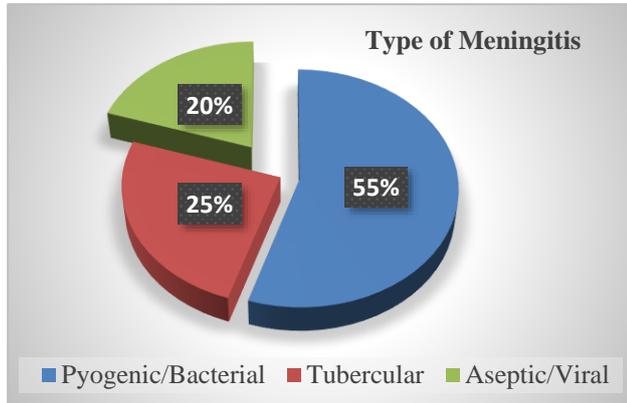
The analysis of presenting signs and symptoms showed that the most common clinical feature which was present in 78 (97.5%) was fever. The other common clinical features were headache (77.50%) vomiting (73.75%) and altered sensorium (63.75%). The common signs present in the studied cases were neck rigidity (71.25%), Brudzinski's sign (68.75%), Kernig's sign (63.75%) and cranial nerve palsies (21.25%) (Table 4).

**Table 4: Signs and symptoms of the studied cases.**

Signs and symptoms	No. of patients	Percentage (%)
<b>Clinical features (symptoms)</b>		
Fever	78	97.50
Headache	62	77.50
Vomiting	59	73.75
Altered sensorium	51	63.75
<b>Signs</b>		
Neck rigidity	57	71.25
Brudzinski's sign	55	68.75
Kernig's sign	51	63.75
Cranial nerve palsies	17	21.25

Amongst 80 studied cases there were 44 (55%) patients who were diagnosed to be having pyogenic meningitis while remaining 36 (45%) patients were having non-pyogenic meningitis. Out of 36 patients with non-pyogenic

meningitis 20 (25%) cases were having tubercular meningitis while remaining 16 (20%) patients were having viral meningitis (Figure 2).



**Figure 2: Type of meningitis in studied cases.**

The CSF analysis was done in all the cases. CSF sugar, protein and cytology reports were analyzed. CSF lactate levels was also done in all the cases. The CSF cytological

examination showed that the mean total cell count was more (643.23±102.02) in pyogenic meningitis as compared to non-pyogenic (viral/tubercular) meningitis (121.76±59.74) and the difference was found to be statistically highly significant (p<0.0001). The differential cell count showed that there was a neutrophilic predominance pattern in pyogenic meningitis cases whereas in non-pyogenic meningitis there was lymphocytic predominance. The difference was found to be statistically significant (p<0.05) (Table 5).

The analysis of CSF sugar, protein and lactate levels showed that the mean CSF sugar levels in pyogenic meningitis cases was 39.12±18.12 mg/dl whereas in non-pyogenic meningitis cases the mean CSF sugar levels were found to be 58.32±15.17 mg/dl. Mean CSF protein levels in pyogenic and non-pyogenic meningitis were found to be 264.62±102.98 mg/dl and 120.76±43.12 respectively. The analysis of CSF lactate levels showed that pyogenic meningitis cases had a significantly high level of CSF lactate as compared to non-pyogenic meningitis cases and the difference was found to be statistically highly significant (p<0.0001) (Table 6).

**Table 5: CSF cytology in studied cases.**

CSF cytology	Total cell count		Polymorphonuclear leukocytes (PMN)		Lymphocytes	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
<b>Pyogenic meningitis</b>	643.23	102.02	74.37	21.98	24.36	9.78
<b>Non-pyogenic meningitis</b>	121.76	59.74	35.14	18.76	64.22	20.12
<b>P value</b>	<0.0001		<0.0001		<0.0001	
<b>Significance</b>	Highly significant		Highly significant		Highly significant	

**Table 6: CSF sugar, protein and lactate levels.**

Analysis	Sugar (mg/dl)		Protein (mg/dl)		CSF lactate	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
<b>Pyogenic meningitis</b>	39.12	18.12	264.62	102.98	12.76	3.02
<b>Non-pyogenic meningitis</b>	58.32	15.17	120.76	43.12	3.58	1.02
<b>P value</b>	<0.0001		<0.0001		<0.0001	
<b>Significance</b>	Highly significant		Highly significant		Highly significant	

**DISCUSSION**

This was a prospective analytical study in which total 80 patients with meningitis were included on the basis of a predefined inclusion and exclusion criteria. Out of the studied cases there were 46 (57.50%) males and 34 (42.50%) females with a male:female ratio of 1:0.739. This male preponderance for the meningitis has also been reported by Bagheri-Nesami et al.<sup>9</sup> The authors conducted a study to assess types, risk factors, clinical symptoms and diagnostic tests of meningitis in hospitalized patients. Of the 137 patients with meningitis, 73 (53.9%) were viral, 61

(46%) bacterial, 1 (0.7%) fungal, and 2 (1.4%) unknown. The majority of risk factors in patients were head trauma, upper respiratory infection, and drug addiction. The most common clinical signs were headache, fever, nausea and vomiting, and stiff neck. The authors found that majority of the affected cases were males (71.5%). Similar male preponderance was also reported by the authors such as Basri et al and Brouwer et al.<sup>10,11</sup>

In our study the mean age of the male and female patients was found to be 38.42±7.12 and 37.46±6.28 years respectively. The mean age of cases in our study was found

to similar to the study conducted by Gudina et al.<sup>12</sup> The authors conducted a hospital based longitudinal study of cases of acute bacterial meningitis. In this study the mean age of the participants was 32.3 years (SD=13.1); 85.6% of them were younger than 50 years. Similar age distribution was also reported by the authors such as Shukla et al and Ihekweba et al.<sup>13,14</sup>

In our study the most common clinical feature which was present in 78 (97.5%) was fever. The other common clinical features were headache (77.50%) vomiting (73.75%) and altered sensorium (63.75%). The common signs present in the studied cases were neck rigidity (71.25%), Brudzinski's sign (68.75%), Kernig's sign (63.75%) and cranial nerve palsies (21.25%). In a prospective study of patients with meningitis Subrahmanyam et al found that fever was the commonest symptom in patients with meningitis and was seen in 91.67% cases.<sup>15</sup> The most common sign in this study was found to be Brudzinski's sign which was seen in 70% of the cases. Fever and neck stiffness was reported to be the common sign and symptom in studies undertaken by Kastenbauer et al and Kleine et al.<sup>16,17</sup>

Finally, we found that there was a significantly high mean CSF cell count in bacterial meningitis as compared to non-bacterial meningitis. Where polymorphonuclear leukocytes (PMN) were predominantly seen in bacterial meningitis and lymphocytes were predominant cells in CSF in cases of non-bacterial meningitis. The mean CSF sugar levels in pyogenic and non-pyogenic meningitis cases was 39.12±18.12 mg/dl and 58.32±15.17 mg/dl respectively. Mean CSF protein levels in pyogenic and non-pyogenic meningitis were found to be 264.62±102.98 mg/dl and 120.76±43.12 respectively. The analysis of CSF lactate levels showed that pyogenic meningitis cases had a significantly high level of CSF lactate as compared to non-pyogenic meningitis cases and the difference was found to be statistically highly significant ( $p < 0.0001$ ). Aro conducted a study of 134 (86 bacterial and 48 viral) patients. Among the bacterial meningitis, 74.42% patients were found to be CSF gram's stain and/or culture positive for bacteria, whereas 25.58% were culture negative.<sup>18</sup> Overall, blood culture was positive in nineteen (29.68%) and negative in forty-five (70.31%) patients. The authors found that the mean CSF lactate level in bacterial meningitis cases amounted to 14.96±6.13 mmol/L with high sensitivity (98.3%) and positive predictive value (73.4%), where as it was significantly lower in the viral group 2.38±0.59 mmol/L. Thus, this study, similar to the finding of our study, concluded that a high lactate level is suggestive of pyogenic meningitis as compared to non-pyogenic meningitis. Similar findings were also reported by Genton et al and Cameron et al.<sup>19,20</sup>

## CONCLUSION

The CSF lactate levels can be used to differentiate between pyogenic and non-pyogenic (viral/tubercular) meningitis.

It is particularly important in cases where gram staining and culture sensitivity doesn't yield positive results.

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