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Original Research Article

Role of cerebrospinal fluid, creatine kinase and lactate dehydrogenase enzyme levels in diagnostic and prognostic evaluation of tubercular and pyogenic meningitis

Abhishek Jha*, Narendra C. Dwivedi, Sujit K. Verma, Ajeet K. Chaurasia

Department of Medicine Moti Lal Nehru Medical College, Allahabad, Uttar Pradesh, India

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***Correspondence:**
Dr. Abhishek Jha,
E-mail: dr.jha.llrmmc@gmail.com

ABSTRACT

Background: Etiological diagnosis for meningitis remains a challenge and often a cerebrospinal fluid (CSF) examination may not give the precise diagnosis. Many enzymes are known to be present in abundance in nervous system. In meningitis, nerve tissue damage leads to release of these enzymes into CSF, which may have important diagnostic and prognostic role. Aim was to evaluate the diagnostic and prognostic significance of creatine kinase (CK) and lactate dehydrogenase (LDH) enzymes in CSF of tubercular and pyogenic meningitis.
Methods: A prospective case control study of 50 subjects with pyogenic or tubercular meningitis, admitted in Department of Medicine, S.R.N. Hospital, M.L.N.M.C. Allahabad, Uttar Pradesh, India from September 2015-August 2016 was done. Level of CK and LDH were estimated in CSF and serum on day of admission and 7th day. 50 subjects with non-neurological diseases were taken as control.
Results: Out of total 50 patients, 36 were of tubercular meningitis and 14 were of pyogenic meningitis. Mean CSF CK and CSF LDH levels were significantly raised in both conditions with respect to controls ($p<0.001$ and $p<0.05$ respectively). Mean CSF CK and CSF LDH level were significantly reduced from day of admission to 7th day in both tubercular and pyogenic meningitis patients.
Conclusions: Enzymes level in CSF like CK and LDH are significantly raised in pyogenic and tubercular meningitis. Accessing its value can be an important diagnostic and prognostic marker.

Keywords: Cerebrospinal fluid, Creatine kinase, Lactate dehydrogenase, Meningitis

INTRODUCTION

Acute infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision-making, and rapid institution of therapy can be lifesaving. These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and infectious thrombophlebitis, etc. Each may present with a nonspecific prodorme of fever and headache, which in a previously healthy individual may initially be thought to be benign, until (with the exception of viral meningitis) altered consciousness, focal neurologic signs, or seizures develop.[1] Meningitis is usually caused by bacteria or viruses, fungal, parasites, but can be a result of injury, cancer, or certain drugs. It is important to know the specific cause of meningitis because the treatment differs depending on the cause.

The brain is naturally protected from the body's immune system by the barrier that the meninges create between

the bloodstream and the brain. Normally, this protection is an advantage because the barrier prevents the immune system from attacking the brain. However, in meningitis, the blood-brain barrier can become disrupted; once bacteria or other organisms have found their way to the brain, they are somewhat isolated from the immune system and can spread. When the body tries to fight the infection, the problem can worsen; blood vessels become leaky and allow fluid, WBCs, and other infection-fighting particles to enter the meninges and brain. This process, in turn, causes brain swelling and can eventually result in decreasing blood flow to parts of the brain, worsening the symptoms of infection.[2]

Since prompt and precise etiological diagnosis remains a challenge and often a thorough cerebrospinal fluid examination may not give a precise diagnosis, a quick and reliable test is required for rapid bedside diagnosis. Brain tissue has a relatively large amount of enzyme activity and elevation of various enzymes in meningitis has been reported and many mechanisms have been postulated.[3-6]

However, no correlation was observed between CSF and serum activities of any of these enzymes. Nevertheless, the prognosis for individual patients cannot be established on the basis of enzymatic activity alone, but depends on several factors.

Therefore, various investigators Aggarwal AP et al, Jain MK et al, Donald PR et al, Yu SZ et al, Pancewicz SA et al, AM Al-Noaemi et al, Maharotra TN et al, Dave KN et al, Knight JA et al, have used them for the diagnosis as well as for determining the prognosis in cases of meningitis.[7-15] However, the role of various CSF enzymes needs to be evaluated as not enough work has been carried out and majority of workers have estimated one of these enzymes either in CSF or serum.

It is in this context that the present study was planned to evaluate the diagnostic and prognostic significance of creatine kinase (CK) and lactate dehydrogenase (LDH) in cases of meningitis by serial estimation of these enzymes in CSF as well as serum in proven cases

METHODS

It was a prospective case study. All patients selected from the patients, admitted in Emergency Medicine Unit [EMU] in Swaroop Rani Nehru Hospital during the course of the study. They examined clinically in detail with special reference to altered level of consciousness, degree of neurological deficits and signs of meningeal irritation.

Selection of case and control

- Patient having classical history of fever, headache, vomiting with or without altered sensorium having signs of meningeal irritation
- Age and sex matched individuals without any evidence of neurological disease served as controls. These patients had minor surgical ailments like hernia or hydrocoele and were operated under spinal anesthesia and CSF samples were taken at that time.

Inclusion criteria

Clinical features suggestive of meningitis.

Exclusion Criteria

Patient suffering from;

- Acute or chronic liver disease
- Neurological disorders like Stroke, ICSOL
- Patient with history of muscles diseases
- Patient suffering from renal diseases.

Study procedure

- All selected subjects underwent detailed neurological examination with special reference to altered level of consciousness, signs of meningeal irritation
- The blood sample collected on the day of admission for estimation of routine and biochemical investigation like complete haemogram, random blood sugar (RBS), serum urea, serum creatinine, liver function test (LFT), electrolyte, urine routine and microscopy. Chest X-ray PA view done in all cases
- The lumbar puncture done on the day of admission and on 7th day. CSF sent for cytological and biochemical examination including the estimation of enzyme activities of CK, LDH.

The diagnosis of PM and TBM was based on biochemical, microscopic examination, relevant staining and culture of the CSF for bacteria, mycobacterium tuberculosis. CSF examination was diagnostic in all cases and only the cases with definitive diagnosis of PM or TBM were included. The diagnosis of TBM was made with CSF low sugar, elevated proteins with lymphocytic pleocytosis and positive evidence of mycobacterium tuberculosis either on CSF Ziehl-Neelsen staining or culture and/or PCR.

All cases of PM had CSF low sugar with evidence of neutrophilic pleocytosis, raised protein and positive evidence the bacteria on Gram's staining or culture and sensitivity.

- Serum CK, LDH also sent on day of admission and on 7^{th} day
- LDH estimated by using LDH (P-L) kit uses the modified IFCC method
- Normal Cut off CSFLDH level <40 U/L
- CK estimated by using CK (NAC act.) kit uses Immunoinhibition/Modified IFCC method

- Normal Cut off CSF CK level <18 U/L
- Details of CSF and serum enzyme values and other investigations collected and analysed and final conclusion derived.

Statistical analysis

The Graph Pad software version 6.0 was used to analyze data. Statistical analysis was done by applying student 't' test. For the comparison of various results within the same group, on different days of hospitalization, the paired 't' test was applied, whereas for the comparison between the two groups of PMs or TBM or meningitis versus control subjects; unpaired 't' test was applied. The level of significance was considered 0.05.

RESULTS

The present observational case control study was conducted on 50 cases admitted to S.R.N. Hospital with meningitis. The mean age of patient was 37.72±16.64 years in case of TBM and 33.21±11.21 years in case of PM, out of which 21 (42%) were male and 15 (30%) were female in case of TBM and 9 (18%) were male and 5 (10%) were female in case of PM.

Table 1: Common clinical features of TBM and PM cases.

Clinical features	TBM patients (n=36)	PM patients (n=14)
	Number/Percent	Number/Percent
Fever	36 (100%)	14 (100%)
Headache	34 (94.4%)	14 (100%)
Vomiting	26 (72.2%)	12 (85.7%)
Meningeal sign	36 (100%)	14 (100%)
Altered sensorium	34 (94.4%)	11 (78.6%)
Focal deficit	05 (13.89%)	0
Cranial nerve palsy	04 (11.1%)	0
Seizure	0	02 (14.2%)

The incidence of TBM was more than PM in both male and female gender. This may be due to the fact that tuberculosis is one of the common infections in UP (India) in lower socioeconomic groups. TBM and PM males (60%) outnumbers the females (40%).

Fever and meningeal sign was present in almost all cases 50 (100%). Headache, vomiting, altered sensorium was present in 48 (96%), 38 (76%), 45 (90%) cases respectively. Focal deficit in form of hemiplegia in 5 (10%) cases, cranial nerve palsy and seizure in 8% and 4% of cases respectively. Altered sensorium, Focal deficit in form of hemiplegia and cranial nerve palsy was found to be more in TBM cases. seizures were more in pyogenic meningitis cases (Table 1).

Table 2: Comparison of CSF enzymes between tubercular and pyogenic meningitis on day of admission.

Enzymes	TBM (n=36)	PM (n=14)	p-value
CK (U/l)	20.38±5.78	22.22±2.80	0.138
LDH (U/l)	123.69±62.66	218.07±59.06	<0.01

CSF enzyme values on 0^{th} day between tubercular and pyogenic meningitis were compared. Mean CSF LDH was significantly higher (p<0.01) in pyogenic meningitis compared to tubercular whereas CSF CK did not show any significant change (p=0.138) (Table 2).

Table 3: Comparison of serum enzymes between tubercular and pyogenic meningitis on 0^{th} day.

Enzymes	TBM (n=36)	PM (n=14)	p-value
CK (U/l)	58.77±18.27	66.50±18.25	0.191
LDH(U/l)	353.84±95.20	351.98±51.08	0.141

Serum enzyme values on 0^{th} day between tubercular and pyogenic meningitis were compared. Mean serum CK and LDH did not show any significant change (p=0.191) and (p=0.141) respectively in pyogenic meningitis compared to tubercular meningitis (Table 3).

Table 4: Mean CSF enzymes in relation to outcome in TBM.

CSF Enzyme	Patient improved (n=25)		p-value	Patient deteriorated* (n=04)		p-value	Patient who died (n=07)	
	0^{th} day	7^{th} day		0^{th} day	7^{th} day		0^{th} day	7^{th} day
CK (U/l)	19.48±4.84	17.28±3.98	0.002	26.35±5.91	24.05±4.19	0.411	20.18±7.53	Not done
LDH (U/l)	96.27±31.24	58.44±18.26	<0.001	125.13±30.37	126.08±30.70	0.886	220.80±66.37	Not done

*Deteriorated means those who develop focal neurologic deficit or cranial nerve palsy or seizures or GCS Scoring.

The mean CSF CK and LDH in patients who improved was 19.48±4.84 U/l and 96.27±31.24 U/l respectively on 0^{th} day and 17.28±3.98 U/l and 58.44±18.26 U/l respectively on 7^{th} day (Table 4). The mean CSF CK and LDH in patients who deteriorated was 26.35±5.91 U/l and 125.13±30.37 U/l respectively on 0th day and

24.05±4.19 U/l and 126.08±30.70 U/l respectively on 7th day (Table 4).

The mean CSF CK and LDH of the patients who died was 20.18±7.53 U/l and 220.80±66.37 U/l on 0th day respectively, but their 7th day value could not be estimated (Table 4).

In patient who improved their mean CSF CK, LDH on 7th day shows significant fall ($p<0.05$) compared to that on 0th day (Table 4). In patient who deteriorated their mean CSF CK and LDH on 7th day compared to that on 0th day did not showed any significant change in both group of patient ($P>0.05$) (Table 4).

Table 5: Mean CSF enzymes in relation to outcome in PM.

CSF Enzyme	Patient improved (n=10)		p-value	Patient deteriorated* (n=02)		p-value	Patient who died (n=02)	
	0th day	7th day		0th day	7th Day		0th day	7th day
CK (U/l)	20.81±1.69	18.06±1.66	<0.01	24.70±0.71	19.75±2.90	0.031	26.80±1.27	Not done
LDH (U/l)	211.48±28.86	71.71±14.56	<0.01	142.00±19.80	125.00±24.04	0.442	327.10±40.87	Not done

*Deteriorated means those who develop focal neurologic deficit or cranial nerve palsy or seizures or GCS scoring.

The mean CSF CK and LDH in patients who improved was 20.81±1.69 U/l, 211.48±28.86 U/l respectively on 0th day and 18.06±1.66 U/l, 71.71±14.56U/l respectively on 7th day (Table 5).

The mean CSF CK and LDH in patients who deteriorated was 24.70±0.71 U/l, 142.00±19.80 U/l respectively on 0th day and 19.75±2.90 U/l, 125.00±24.04 U/l respectively on 7th day (Table 5). Patients who died their mean CSF CK and LDH was 26.80±1.27 U/l, 327.10±40.87 U/l on 0th day but their 7th day value could not be estimated (Table 5).

In patients who improved their mean CSF CK, LDH on 7th day shows significant fall ($p<0.01$ and $p<0.01$) respectively compared to that on 0th day. In patient who deteriorated the mean CSF CK on 7th day also shows significant fall ($p=0.031$) compared to that on 0th day, but CSF LDH did not showed any significant change (Table 5).

DISCUSSION

The measurement of CSF LDH has been recently advocated in establishing an early diagnosis of meningitis, as well as being of some value in separating this entity from aseptic meningitis. Our data shows the mean CSF LDH value was significantly raised than in control on 0th day in both TBM and PM ($p<0.01$) and it declined significantly on 7th day in both TBM ($p<0.001$) and PM ($p<0.01$) in all those cases who have improved.

This was similar to observation made by Kepa L et al, Sharma et al, Knight JA et al, Patro et al, AP Aggarwal et al, PR Donald et al.[7,9,15-18]

The LDH activity in CSF in PM significantly ($p<0.01$) is higher than in TBM. This was similar to, Sharma et al, Aggarwal AP et al, and Jain et al, this indicate that higher level of CSF LDH favours the diagnosis towards PM.[7,8,17] Although the number of cases studied in our case was relatively small, it is believed that it has significant value in diagnosis of early meningitis and differentiate between PM and TBM.

The LDH value have declined significantly on the 7th day compared to that on 0th day ($p<0.01$) in both TBM and PM in all those cases who have survived. This would mean that during the first few days there is acute inflammation of the meninges and the pathological process at its peak. Once the patient is treated there is clearance in vascularity of the meninges and the enzymatic activity.

The CSF CK was estimated in patients of TBM and PM on 0th and 7th day. Mean CSF CK was significantly elevated compared to control ($p<0.05$) on 0th day. This observation was similar in both TBM and PM. Our observation was similar to the observation made by Sharma et al, Yaser et al, Pancewicz SA et al, Patil B et al.[11,12,17,19] But there was no correlation between the CSF and serum CK activity. However, the serum CK was much higher than CSF in both control, TBM, PM on the 0th day. The CSF CK value in PM was not significantly higher than in TBM (p-value=0.138) on 0th day, which was contrary to study of Sharma et al and Patil B et al.[17,19]

The prognosis and the efficacy of treatment for individual patient could not be established on the basis of enzymatic activity. Rise in enzymatic activity in the serum cannot be explained on the basis of disturbed BBB, as the enzymatic activity is normally very low in CSF in comparison to serum. Further several studies have shown that when BBB is intact the enzymatic activity is unaffected by serum changes. Out of 50 patients taken

into study death occurred in 7 cases of TBM and 2 cases of PM. All the death occurred within 0th to 5th day and hence their 7th day value could not be estimated. The basal enzymatic activity of CSF LDH in all these nine cases that died was higher as compared to those who improved. This was similar to study of Sharma et al.[17]

Six cases of TBM and PM gradually deteriorated symptomatically in form of development of cranial nerve palsy, focal neurologic deficit, convulsion or GCS scoring and their 7th day enzyme level was estimated in CSF.

In present study mean CSF LDH and CK levels have shown significant fall on 7th day compared to that on 0th day (p-value<0.05) in patient showing improvement in both TBM and PM cases. This was similar to Sharma et al, Patro et al.[17,18] The rate of fall of enzymes level was different in those cases who improved and that deteriorated. Patient who deteriorated there was no significant fall of CK and LDH level seen in both BM and TBM group. This was contrary to the study of Patro et al.[18]

This signified that level of fall of CSF CK and LDH level helps in understanding the prognosis of PM and TBM. Further the CSF enzymatic activity correlated better than the serum with the clinical status of the patient.

CONCLUSION

Inspite of many advents of sophisticated methods of investigations, diagnosis of meningitis remains a puzzle for physicians. In this eastern zone of state of Uttar Pradesh, India meningitis is no way less in comparison to other parts of country. In present study CSF enzymes like LDH and CK which remain significantly high compared to controls, hence their estimation gives an important clue to the diagnosis of meningitis. The enzymatic activity of LDH significantly raised in PM compared to TBM this indicates that higher level of CSF LDH favours the diagnosis towards PM but there was no cutoff level to differentiate them.

The cases where the fall in enzymatic activity was faster, improved early as compared to those where the fall was slow. Further the CSF enzymatic activity correlated better than serum with the clinical status of the patients. The CSF LDH and CK level may be helpful in prognosis of meningitis, hence the study is of prognostic significance as higher basal activity and serial rise were associated with poor prognosis. However, no correlation was observed between CSF and serum activities of these enzymes. Nevertheless, the prognosis for individual patients cannot be established on the basis of enzymatic activity alone, but depends on several factors. Therefore, LDH and CK activities in CSF have been used to predict prognosis Diagnosis of meningitis and to estimate the efficacy of treatment.

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