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Original Article

Internal Medicine Section

Role of CSF CK, LDH, GGTP Enzyme Levels in Diagnostic and Prognostic Evaluation of Meningitis

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ABSTRACT

Background: Aetiological diagnosis for meningitis remains a challenge and often a thorough Cerebrospinal fluid (CSF) examination may not give a precise diagnosis as at times CSF findings may simulate meningitis like picture as in carcinomatous meningitis, chemical meningitis, early stages of Guillan bare syndrome, subarachnoid hemorrhage, ICSOL, brain abscess, intracranial extension of epidural or subdural infection. Lesions of tissue rich in enzymes may cause enzymatic release on tissue destruction, so also in meningitis and many enzymes are known to be present in abundance in nervous system.

Aim: To evaluate the diagnostic and prognostic significance of Creatine Kinase (CK), Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transpeptidase (GGTP) enzymes in CSF of meningitis.

Materials and Methods: A prospective cases control study of pyogenic and tubercular meningitis patients of 44 cases admitted in department of medicine from September 2011-September 2012 was done. Enzymes like CK, LDH and GGTP were estimated on day 0 (day of admission) and 7th day in the CSF and in serum. CSF and serum CK, LDH, GGTP was estimated on 0th day 0 only in cases of controls.

Result: Out of 44 patients, total 32 were tubercular meningitis and 12 were pyogenic meningitis. Mean CSF CK, LDH levels were significantly raised in both conditions with respect to controls in day 0 with $p < 0.0001$ and $p < 0.05$ respectively. Mean CSF CK, LDH level were also significantly reduced from 0 to 7th day in both tubercular, pyogenic meningitis, while CSF GGTP was not significantly raised with respect to control in day 0.

Conclusion: Enzymes level in CSF like CK, LDH are significantly raised in the meningitis and accessing its value can be an important diagnostic and prognostic marker. But more studies are required to establish the usefulness of estimating these enzymes.

Keywords: Creatine kinase, Cerebrospinal fluid, Gamma glutamyl transpeptidase, Lactate dehydrogenase, Meningitis

INTRODUCTION

Infectious disease remains a major cause of death and disability for millions of people around the world, despite decades of dramatic progress in their treatment and prevention. A careful history is essential and must include details on underlying chronic diseases, medications, occupation, and travel. Risk factors for exposure to certain types of pathogens may give important clues to diagnosis.

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 prodrome 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].

The central nervous system (CNS) may appear protected from perturbations in the environment by a blood brain barrier – a system of tight junction around capillaries that resist the entry of pathogens, inflammatory cells and macromolecules into the subarachnoid space and the brain. However, the barrier fails to resist the intensity of the microbial world and its presence also cause difficulty in the delivery of antimicrobial agents in adequate concentrations.

Meningitis is the most common sequel to microbial invasion of the CNS. Neurological sequalae are serious and rather common among survivors [2]. It is one of the dreadful infectious diseases and more common in developing countries than developed countries. So, early diagnosis and treatment remains a challenge to the clinician.

Besides routine cerebrospinal fluid analysis (protein, sugar, and cell count), other additional tests like latex agglutination, counter-immuno electrophoresis, radio - immunoassay and measurement of CSF lactate have been utilised with varying degrees of success for the diagnosis of bacterial meningitis. The limitation of these options is however considerable as some require specific antisera and some are too slow and laborious procedures. More over no single test mentioned above could achieve a high degree of sensitivity and specificity required for a definitive diagnosis.

The culture of CSF which gives a definite diagnosis and most importantly the antibiotic sensitivity pattern of the infecting organism, takes longer time. More over CSF culture for pyogenic organisms are positive only in 30%-60% [3].

Since prompt and precise aetiological 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. Many enzymes are known to be present in abundance in the nervous system. Meningitis disturbs the blood brain barrier (BBB) and is expected to cause rise in enzymatic activity. Therefore, various investigators Aggarwal AP et al., [4], Jain MK et al., [5], Donald PR et al., [6], Yu SZ et al., [7], Pancewicz SA [8] have used them for the diagnosis as well as for determining the prognosis in cases of meningitis. 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), Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transpeptidase (GGTP) in cases of meningitis by serial estimation of these enzymes in CSF as well as serum in proven cases.

AIM OF THE STUDY

To evaluate the diagnostic and prognostic significance of CK, LDH and GGTP enzymes in CSF of Meningitis.

MATERIALS AND METHODS

Patients admitted to Medicine department of SCB Medical College and Hospital, Cuttack (India) from Sept 2011 - Sept 2012 with clinical features suggestive of meningitis within 48h of onset of symptoms and not being treated earlier were taken into study.

Based on clinical manifestation and laboratory results of CSF which include glucose as well as protein concentration, qualitative and quantitative cytology, Gram stain, ZN stain, 44 number of patients were finally selected for study which were diagnosed as either Pyogenic or Tubercular Meningitis.

Patient suffering from liver, muscle, cardiac, renal disease, neurological disorders like Stroke, ICSOL and trauma, patients on antipsychotics and antiepileptic drugs, pregnancy and females on oral contraceptive pills were excluded from the study.

Twenty two, age and sex matched individuals without any evidence of neurological disease and with minor surgical ailments like hernia, hydrocele, etc who are to be operated under spinal anaesthesia were taken as controls. The CSF was collected during the time of spinal anaesthesia.

All patients were examined clinically in detail with special reference to altered level of consciousness, degree of neurological deficits and signs of meningeal irritation.

The blood sample was sent on 0^{th} day 0 0 (day of admission) for estimation of routine and biochemical investigation like complete Haemogram, RBS, Blood urea, serum Creatinine, LFT, serum sodium and potassium. Chest X – ray was done routinely in all cases.

CT scan of brain was done in all cases of meningitis to exclude other neurological conditions like stroke, cranial nerve palsy, brain abscess, hydrocephalus and to detect evidence of raised intracranial pressure. The lumbar puncture was done and CSF was sent for cytological and biochemical examination including the estimation of enzyme activities of CK, LDH, GGTP was done on day 0. Serum CK,LDH,GGTP was also done on 0^{th} day 0 0.

The procedure was repeated on 7^{th} day and CSF and serum sample was sent for estimation of enzymes like CK, LDH, GGTP in patients. The CSF and blood samples of controls were collected during spinal anaesthesia of minor surgical procedure and were sent for estimation of same enzyme activity.

LDH was estimated by using LDH kit and Biolis 24i – 36 Tray based on SCE recommended method.

CK was estimated by using CK kit based and Biolis 24i – 36 Tray on IFCC methodology.

GGTP was estimated by using the GGT kit and Biolis 24i – 36 Tray based on Szasz methodology.

Details of CSF and serum enzyme values and other investigations were collected and analysed and final conclusion was derived. Statistical analysis was done applying the paired and unpaired student t- test using software Instat 3 and SPSS.

OBSERVATION

Out of 114 meningitis patient admitted to Department of Medicine during the period September 2011 to September 2012, finally 44 numbers of cases selected for study after screening by exclusion criteria.

[Table/Fig-1] shows the gender distribution of meningitis cases. Out of 44 number of cases 29(65.9%) were male and 15(34.1%) were female. Out of 29 male patients 21(47.7%) were of tubercular and 8(18.2%) were pyogenic. Out of 15 female patients 11(25%) were of tubercular and 4(9.1%) were pyogenic.

[Table/Fig-2] shows the common symptoms and signs of tubercular and pyogenic meningitis cases. Fever and meningeal sign was present in almost all cases 44(100%). Headache, vomiting, altered sensorium was present in 36(81.8%), 25(56.8%), 21(47.72%) cases respectively. Focal deficit in form of hemiplegia in 9.1% cases, cranial nerve palsy and seizure in 9.1 % and 6.81% of cases respectively. Focal deficit in form of hemiplegia and cranial nerve palsy was found to be more in TBM cases. Altered sensorium and seizures was more in pyogenic meningitis cases.

[Table/Fig-3] shows the comparison of CSF enzyme values on 0^{th} day 0 0 between tubercular and pyogenic meningitis. Mean CSF CK and LDH was significantly higher ($p < 0.0001$) and ($p < 0.005$) respectively in pyogenic meningitis compared to tubercular whereas CSF GGTP did not show any significant change ($p = 0.826$) between them.

[Table/Fig-4] shows the comparison of serum enzyme values on 0^{th} day 0 0 between tubercular and pyogenic meningitis. Mean serum CK and LDH was significantly higher ($p < 0.05$) and ($p < 0.005$) respectively in pyogenic meningitis compared to tubercular whereas serum GGTP did not show any significant change ($p = 0.0716$) between them.

[Table/Fig-5] shows the mean CSF enzymes in relation to outcome in TBM. The mean CSF CK, LDH, GGTP in patients who improved was 49.54 $\pm$ 20.2 U/l, 192.9 $\pm$ 65.52 U/l, 21.22 $\pm$ 10.24 U/l respectively on 0^{th} day 0 0 and 27.3 $\pm$ 10.4 U/l, 111.5 $\pm$ 42 U/l, 19 $\pm$ 3.5 U/l respectively on 7^{th} day. The mean CSF CK, LDH, GGTP in patients who deteriorated was 54.3 $\pm$ 21.1 U/l, 187 $\pm$ 61.65

Type	Male	Female	Total
TBM	21(47.7%)	11(25%)	32
PM	08(18.2%)	4(9.1%)	12
Total	29	15	44

[Table/Fig-1]: Gender distribution of meningitis cases (n = 44)

Clinical features	TBM patients (n=32)	PM patients (n=12)
	Number/Percent	Number/Percent
Fever	32(100%)	12(100%)
Headache	24(75%)	12(100%)
Vomiting	22(68.75%)	03(25%)
Meningeal sign	32(100%)	12(100%)
Altered sensorium	14(43.75%)	07(58.33%)
Focal deficit	04(12.5%)	0
Cranial nerve palsy	04(12.5%)	0
Seizure	0	03(25%)

[Table/Fig-2]: Common clinical features of TBM and PM cases

Enzymes	TBM (n=32)	PM (n=12)	p-value
CK (U/l)	51.81 ± 19.9	87.17 ± 16.46	<0.0001
LDH(U/l)	199.71 ± 74.16	271.4 ± 80.07	<0.005
GGTP(U/l)	19.56 ± 9.01	20.16 ± 4.63	0.826

[Table/Fig-3]: Comparison of CSF enzymes between tubercular and pyogenic meningitis on 0^{th} day 0 0

Enzymes	TBM (n=32)	PM (n=12)	p-value
CK(U/l)	234.12 ±40.19	267.9 ± 43.31	<0.05
LDH(U/l)	307.69 ±61.57	393.83±82.34	<0.005
GGTP(U/l)	39.53±6.07	43.25±5.56	0.0716

[Table/Fig-4]: Comparison of serum enzymes between tubercular and pyogenic meningitis on 0^{th} day 0 0

U/l, 15.6 ± 4.06 U/l respectively on 0th day 0 and 25.12 ± 6.0 U/l, 102.3 ± 34.81 U/l, 15.6 ± 4.06 U/l respectively on 7th day. Patients who died their mean CSF CK, LDH, GGTP was 66.5 ± 9.19 U/l, 325 ± 141.4U/l,17 ± 1.41 U/l on 0th day 0 but their 7th day value could not be estimated. In patient who improved their mean CSF CK, LDH on 7th day shows significant fall ($p < 0.0001$) compared to that on 0th day 0. In patient who deteriorated their mean CSF CK, LDH on 7th day also shows significant fall ($p < 0.005$) compared to that on 0th day 0. But GGTP did not showed any significant change in both group of patient.

[Table/Fig-6] shows the mean CSF enzymes in relation to outcome in PM. The mean CSF CK, LDH, GGTP in patients who improved was 83 ± 13.3 U/l, 221 ± 41.7 U/l, 20.3 ± 2.9 U/l respectively on 0th day 0 and 26.1 ± 5.88 U/l, 107.6 ± 36.4 U/l, 21.33 ± 9.33 U/l respectively on 7th day. The mean CSF CK, LDH, GGTP in patients who deteriorated was 94.6 ± 6.11 U/l, 371.6 ± 39.5 U/l, 20.6 ± 5.03 U/l respectively on 0th day 0 and 36.3 ± 14.3 U/l, 150.6 ± 67 U/l, 17.3 ± 3.05 U/l respectively on 7th day. Patients who died their mean CSF CK, LDH, GGTP was 88 ± 29.45 U/l, 271.6 ± 82.8 U/l, 19.33 ± 8.32 U/l on 0th day 0 but their 7th day value could not be estimated. In patients who improved their mean CSF CK, LDH on 7th day shows significant fall ($p = 0.0002$ & $p < 0.005$) respectively compared to that on 0th day 0. In patient who deteriorated the mean CSF CK, LDH on 7th day also shows significant fall ($p < 0.05$) compared to that on 0th day 0. But GGTP did not showed any significant change in both group of patient.

meningitis classically present with fever, headache, and signs of meningeal irritation, with or without altered consciousness [10]. In a study by Van de Beek et al., [11] have seen most patients having at least two of the symptoms like headache, fever, neck stiffness and altered mental status. In a study by RS Illingworth [12], 28% reported headache, 25% had vomiting, 13% had fever. Infarcts occur in about 30% of cases, commonly in the internal capsule and basal ganglia, causing a range of disorders from hemiparesis to movement disorders [13]. Our study shows higher incidence of headache, fever and vomiting with lesser incidence of neurologic deficit.

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. GGTP is the key enzyme of neural cell membrane and is responsible for transfer of amino acids through the cell membrane. LDH is a zinc-containing enzyme and CK is an intracellular enzyme released in various neurological conditions including infections and increase in their CSF levels reflects the extent of brain injury.

It has been suggested that pathological process that permits blood and plasma to reach the spinal fluid results in increased enzymatic activity by virtue of the contribution of enzyme from plasma. In cases of acute meningitis there is increased outflow from serum due to injury to the blood brain barrier (BBB) resulting into exudation of plasma proteins, enzymes along with circulating leucocytes into spinal fluid [14]. The enzymatic activity in CSF has been reported

CSF Enzyme	Patient improved (n=06)		p-value	Patient deteriorated* (n=03)		p-value	Patient who died (n=03)	
	0th day 0	7th Day		0th day 0	7th Day		0th day 0	7th Day
CK(U/l)	49.54 ± 20.2	27.3 ± 10.4	<0.0001	54.3 ± 21.1	25.12 ± 6.0	<0.005	66.5 ± 9.19	Not done
LDH(U/l)	192.9 ± 65.52	111.5 ± 42	<0.0001	187 ± 61.65	102.3 ± 34.81	<0.005	325 ± 141.4	Not done
GGTP(U/l)	21.22 ± 10.24	19 ± 3.5	0.345	15.6 ± 4.06	16.37 ± 3.37	=0.497	17 ± 1.41	Not done

[Table/Fig-5]: Mean CSF enzymes in relation to outcome in TBM. *Deteriorated means those who develop focal neurologic deficit or cranial nerve palsy or seizures

CSF Enzyme	Patient improved (n=06)		p-value	Patient deteriorated* (n=03)		p-value	Patient who died (n=03)	
	0th day 0	7th Day		0th day 0	7th Day		0th day 0	7th Day
CK(U/l)	83 ± 13.3	26.1 ± 5.88	0.0002	94.6± 6.11	36.3 ± 14.3	< 0.05	88 ± 29.45	Not done
LDH(U/l)	221 ± 41.7	107.6 ± 36.4	< 0.005	371.6± 39.5	150.6 ± 67	< 0.05	271.6 ± 82.8	Not done
GGTP(U/l)	20.3 ± 2.9	21.33 ± 9.33	0.824	20.6 ± 5.03	17.3 ± 3.05	= 0.3823	19.33 ± 8.32	Not done

[Table/Fig-6]: Mean CSF enzymes in relation to outcome in PM

DISCUSSION

The mean age of patient was 35.43 ± 15.02 years in case of TBM and 39.5 ± 16.23 years in case of PM, out of which 21(47.7%) were male and 11(25%) were female in case of TBM and 8(18.2%) were male and 4(9%) were female in case of PM. In a study conducted by Sharma et al., [9], the mean age of patient was 35.12 ± 14.4 years. The age incidence varies as per locality and the category of patients admitted to the hospital.

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 infection in Odisha (India) in lower socioeconomical groups. In both type of meningitis male outnumber the females.

Fever and meningeal sign was the commonest presenting symptoms (100%) in both TBM and PM. Headache was more common in PM (100%) than in TBM (75%). Fever in meningitis is due to release of interleukins like IL-1,8 and TNF – α. Meningeal sign is due to meningeal irritation due to inflammation of meninges which resist the passive flexion. Headache is due to raised intracranial tension stretching the meninges. Focal neurological deficit and cranial nerve palsy and seizure were not seen commonly in our study. This may be due to the fact that most of the cases selected were in early stage before intracranial tension was raised and the early treatment was instituted. In immunocompetent adults acute

to be appreciably less than serum in normal subjects as well as in majority of disorders of central nervous system. However, its activity is elevated in CSF in cases of meningitis and most workers believe BBB is more likely cause for this rise.

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 ($p < 0.0001$) on 0th day 0. This observation was similar in both TBM and PM. Our observation was similar to the observation made by Sharma et al., [9], Yaser et al., [15], Pancewicz SA [8]. 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 0.

The CK value have declined significantly on the 7th day compared to that on 0th day 0 ($p < 0.0001$) 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 value in TBM was significantly higher than in PM ($p < 0.0001$) on 0th day 0. But this do not co-relate with the prognosis.

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.

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 0 in both TBM and PM ($p < 0.0001$) and it declined significantly on 7th day in both TBM ($p < 0.0001$) and PM ($p = 0.0002$) in all those cases who have survived. This was similar to observation made by Kepa L et al., [16], Sharma et al., [9], JA Knight et al., [17]. The LDH activity in CSF in PM is significantly higher ($p <0.005$) than in TBM. The LDH isoenzyme studies carried out in cases of bacterial meningitis have shown that the isoenzyme pattern is primarily a reflection of the presence or absence of leukocytes, and of the predominant type of cell present [18]. 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.

In our study the mean CSF and serum GGTP did not show any significant change neither in TBM nor in PM cases compared to controls on 0th day 0. There was no significant change of CSF or serum GGTP level on 7th day compared to that on 0th day 0 in both TBM and PM. In other studies conducted by Nand et al., [19], Sharma et al., [9], showed significant elevation of GGTP in both TBM and PM cases which is in contrary to our study.

Out of 44 patients taken into study death occurred in 2 cases of TBM and 3 cases of PM. All the death occurred with in 0th to 5th day and hence their 7th day value could not be estimated. Eight cases of TBM and three cases of PM gradually deteriorated symptomatically in form of development of cranial nerve palsy, focal neurologic deficit, convulsion and their 7th day enzyme level was estimated in CSF. They were not followed up further for our study and they were given additional drugs. In our study mean CSF CK, LDH levels have shown significant fall on 7th day compared to that on 0th day 0 in patient showing improvement in both TBM and PM cases. The rate of fall of enzymes was also similar in those cases that deteriorated. This means that the higher basal enzyme level shows better response to treatment. Further the CSF enzymatic activity correlated better than the serum with the clinical status of the patient.

In our study, TBM cases with higher initial CSF CK level deteriorated, on the contrary the cases with higher initial CSF LDH value showed improvement. But higher initial CSF CK, LDH value in PM cases deteriorated. Therefore, due to discordance of observation of these CSF enzyme levels cannot be used as reliable indicator to predict the prognosis in case of meningitis. Further there was poor correlation between CSF and serum enzymatic activity ($r = 0.1966$). Although, the activity of all the CSF CK, LDH enzymes are seen in pyogenic than in tubercular meningitis and activity was higher in serum than in CSF but there was no cut off value to differentiate between TBM and PM. Therefore, CSF enzyme level estimation cannot determine the aetiology of meningitis. However, GGTP levels did not show any significant change in CSF levels in patient showing improvement or deterioration.

CONCLUSION

Inspite of many advent of sophisticated methods of investigations diagnosis of meningitis remains a puzzle for physicians. In this eastern zone of state of Odisha (India) meningitis is no way less in comparison to other parts of country. In our study CSF enzymes like CK, LDH which remain significantly high compared to controls, hence their estimation gives an important clue to the diagnosis of meningitis. The enzymatic activity of CK, LDH although significantly raised in PM compared to TBM but there was no cutoff level to differentiate them. Hence, their estimation cannot predict the aetiology of meningitis. The CSF enzymes also does not give any information about the prognosis of meningitis.

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