Research Article

Role of cerebrospinal fluid lactate dehydrogenase and creatine phosphokinase in the differential diagnosis of bacterial, viral, and tubercular meningitis

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ABSTRACT

Background: Meningitis is a common clinical problem, caused by various bacteria and viruses. Its etiology needs to be ascertained swiftly to institute appropriate therapy to prevent morbidity and mortality. In some cases, the precise etiological diagnosis cannot be ascertained in spite of thorough work up. **Objectives:** The present study was a prospective study undertaken in cases of meningitis admitted in the Medicine Ward of Burdwan Medical College and Hospital to determine the levels of cerebrospinal fluid (CSF) lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) concentration and their possible roles in the etiological diagnosis of different kinds of meningitis. **Materials and Methods:** A prospective study was conducted on 150 patients, 50 patients of each of bacterial, viral, and tubercular meningitis, admitted in the Medicine Ward of Burdwan Medical College and Hospital. The values of CSF CPK, and LDH were calculated for each patient and variation of means was analyzed by appropriate biomedical software. The SPSS for the Windows 20.0 statistical package program has been used in the evaluation of the data. The quantitative data of the groups were compared using ANOVA with *post hoc* test for comparison. $P < 0.05$ was considered statistically significant. **Results:** It was found that CSF LDH, and CPK were significantly elevated in pyogenic meningitis and tubercular meningitis as compared to viral meningitis. The differences between the CSF LDH, and CSF-CPK values in differentiating any one of the three forms against another were found to be statistically significant. **Conclusion:** Thus, CSF CPK and LDH may serve as an useful marker for differentiation of etiology of meningitis at least in conjunction with the classical CSF markers and especially in the doubtful cases.

KEY WORDS: Meningitis; Creatine Phosphokinase; Lactate Dehydrogenase

INTRODUCTION

Meningitis is an inflammation of the meninges that is the protective membrane covering the brain and spinal cord, leading to several clinical patterns. Pathogens reach the meninges by the blood stream or occasionally by spreading from nearby sites such as the middle ear or nasal sinuses. The infection may be caused by infection with virus, bacteria, *Mycobacterium tuberculosis*, or other organisms and less commonly by certain drugs. Among all these, acute pyogenic meningitis is the most common form of suppurative central nervous system (CNS) infection which occurs throughout the world.[1,2]

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It is generally accepted that cerebrospinal fluid (CSF) reflects the metabolism of brain and spinal cord. Lesions of these tissues rich in enzymes correspond with their damage or structural destruction and may cause enzymatic release.[2]

It is known that enzymes have a diagnostic role in the diagnosis of disease, and the increase or decrease of an

enzyme activity than its normal value would be a good marker for many diseases. Recent studies indicate that creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) are two such markers that can be used in the diagnosis of different pathogens.[3,4]

Increased enzymes levels in CSF LDH, and CPK have been reported to indicate tissue damage of the CNS or altered permeability of barriers.

Elevated levels of the enzymes in CSF are usually not associated with elevated serum enzyme levels. Valuable information concerning CSF LDH, and CPK activity relative to duration and severity of clinical signs is available in the medical literature.[5]

If meningitis is not diagnosed promptly with proper etiological diagnosis and appropriate treatment is not started early, it ends fatally with increased morbidity and mortality.

However, sometimes, the prompt precise differentiation between various forms of meningitis is difficult even in adequately equipped hospitals.

Patients with meningitis present themselves with varying and overlapping clinical features of both bacterial and aseptic/viral meningitis which makes it difficult to distinguish them in initial presentation of the patient.

Different laboratory test has different specificity and sensitivity and may take a long time to come to aid the diagnosis. The cost of this uncertainty may be considerable in terms of prolonged hospitalization, the potential hazards of needless chemotherapy, and disquieting epidemiological implication.

Even after full assessment of the clinical picture, careful examination of CSF, Gram's stain and Z-N stain, complete differential count, and measurement of the CSF glucose and protein levels, diagnosis is sometimes in doubt. The situation is further muddled by the trend of prior treatment with insufficient and improper antibiotics.

In pyogenic meningitis, the CSF Gram's stain may be negative due to low number of organisms in many cases. The patients with aseptic meningitis may present with a predominance of polymorphonuclear leukocytes in the CSF during the first 24 hours of illness, thus making difficult to distinguish aseptic meningitis from bacterial meningitis.

CSF LDH, and CPK are produced by bacterial infection and tissue damage and are not affected by blood LDH or CPK concentration and have an advantage over CSF glucose in differentiating bacterial meningitis and tubercular meningitis from aseptic meningitis. CSF LDH, and CPK levels are a rapid, reliable, and inexpensive method for early differentiation of various types of meningitis.

In our study, we will measure lactic dehydrogenase (LDH), CPK in CSF of various types of meningitis cases with an aim to find out their diagnostic significance in cases of meningitis.

If a diagnostic test such as LDH and CPK in CSF give added information regarding early diagnosis in collaboration with other traditional tests, it may be easier to start specific treatment of this deadly disease and prevent morbidity and mortality.

The present study will be undertaken in cases of meningitis to determine the relationship between - the level of CSF, LDH, and CPK concentration and their possible roles in the etiological diagnosis of different kinds of meningitis.

MATERIALS AND METHODS

Study Population

Patients admitted in the General Medicine Ward in Burdwan Medical College and Hospital in the age group of 15–60 years.

Inclusion Criteria

The following subjects in place of criteria are included in the study:

- Patient within the age group of 15–60 years.
- Both male and female patients.
- Clinically and neurologically suggestive of meningitis.

Exclusion Criteria

The following subjects in place of criteria are excluded from the study:

- Presence of another focus of infection in addition to meningitis or any other previously known severe systemic illness/malignancy.
- Conditions which can contribute in elevation of CSF LDH, and CPK level such as CNS tumor, stroke, brain trauma, subarachnoid hemorrhage, and seizure disorder.
- Patients suffering from muscle disorder and myopathy.
- Patients with fungal meningitis.
- HIV and/or on immunosuppressive therapy.

Study Period

The study duration was from March 2016 to August 2017.

Sample Size

A total of 150 patients diagnosed as meningitis (bacterial, tubercular, and viral).

Sample Design

The sample had been designed and classified into three groups: According to detailed history taking, careful clinical examination and CSF analysis.

- 50 patients of bacterial meningitis.
- 50 patients of viral meningitis.
- 50 patients of tubercular meningitis.

Consecutive samples were taken till desired size was reached.

Study Design

This was a prospective study.

Parameters to be Studied

a. History and clinical examination of the patients.
b. Imaging evaluation: CXR and computed tomography (CT) scan brain.
c. CSF examination: (1) Physical examination - appearance, turbidity, etc. (2) Biochemical examination - protein, sugar, and ADA. (3) Cellular study - cell type, cell count, and stain - Gram stain and Z.N stain.
d. Parameters for specific objective: Estimation of CSF LDH, and CPK level.

Study Technique

Data collection

Those cases admitted with features of fever, headache, vomiting, altered sensorium, photophobia, and with or without convulsion in the age group of 15–60 years were examined in detail for any clinical evidence of meningitis. Clinically evident cases of meningitis were randomly selected and submitted for detailed history and careful physical examination. In the clinical evaluation, special attention was given for detection of any other associated pyogenic infection, or ear discharge, h/o contact with tuberculosis, significant history.

Lumbar puncture and CSF study

After detailed clinical (general survey, neurological, and systemic examination), fundus examination, and CT scan of brain, lumbar puncture was performed before initiation of specific antimicrobial agents. Routine and special parameters including LDH and CPK level are measured.

The CSF was obtained by lumbar puncture under strict aseptic way in every case.

CSF collected in the test tubes was used for the following purpose:

1. Color and appearance by naked eye examination.
2. Total cell counting was done immediately after collection in Neubauer's counting chamber. The total cells were counted and the number of polymorphonuclear leukocytes and lymphocytes was noted.
3. 3.2 ml of CSF in the second test tube was centrifuged, and the supernatant was decanted off to another test tube and was used for the estimation of sugar and protein in biochemistry laboratory.

The deposit found after decanting off the supernatant was used as follows:

1. Three smears are prepared; one is used for Gram staining to identify the presence of any Gram-positive or Gram-negative organism.
2. The second smear was stained with Ziehl–Neelsen stain to identify the presence of acid-fast bacilli by carefully searching in light microscope under oil-immersion lens.
3. Another smear was used for differential count of cells 3 ml of CSF in the third test tube was immediately taken to the microbiology department for culture.

CSF LDH, and CPK were measured by standard spectrophotometric methods.

Diagnosis of Bacterial, Viral, and Tuberculous Meningitis

Bacterial meningitis

Diagnosis based on (a) clinical presentation: (1) Acute onset fever, headache, photophobia, vomiting, and neck stiffness and (2) signs of meningeal irritation. (b) CSF findings: (1) White blood cell (WBC) >50/cumm, often greatly increased, predominance of polymorphonuclear lymphocytes, (2) protein: 100–250 mg%, (3) glucose: 20–50 mg%, usually lower than half of blood glucose level, and (4) Gram stain shows organism.

Tuberculous meningitis

Diagnosis based on (a) clinical presentation: (1) Insidious or subacute onset of headache, fever, vomiting, and ill health and (2) signs of meningeal irritation. (b) CSF findings: (1) WBC >25–200/cumm, prominent cell being lymphocytes, (2) protein: 100–1000 mg, (3) glucose: <50, often markedly reduced, (4) tubercle bacilli may be demonstrable in the films or culture, and (5) ADA: >5 IU/L. (c) Supportive evidence: (1) Tuberculous infection elsewhere in the body and (2) radiological evidence of pulmonary tuberculosis.

Viral meningitis

Diagnosis based on (a) clinical presentation: (1) Acute onset fever, headache, photophobia, vomiting, and neck stiffness and (2) signs of meningeal irritation. (b) CSF findings: (1) Pleocytosis, WBC 10–100/cumm, (2) protein: 50–200 mg%, and (3) glucose: Normal (45–80 mg/dl) or 2/3rd of blood glucose or slightly reduced.

The study has been approved by local ethical committee of our hospital.

Data Analysis

At the end of the study, the data will be compiled, tabulated, and analyzed for variation of means and correlation by appropriate biomedical software. The SPSS for the Windows 20.0 statistical package program has been used in the evaluation of the data. The quantitative data of the groups were compared using ANOVA with *post hoc* test for comparison. $P < 0.05$ was considered statistically significant. The study has been approved by local ethical committee of our hospital.

RESULTS

The mean CSF LDH are 280.94 ± 74.488/dl (95% confidence interval [CI]: 261.60–300.48) for pyogenic meningitis, 171.24 ± 211.58 mg/dl (95% CI: 171.24–211.58) for tubercular meningitis, and 35.60 ± 10.394 mg/dl (95% CI: 32.58–38.36) for viral meningitis. This difference between CSF LDH is statistically significant between all groups [Tables 1 and 2].

The mean CSF CPK are 88.76 ± 15.083 mg/dl (95% CI: 84.66–93.08) for pyogenic meningitis, 50.94 ± 18.7164 mg/dl (95% CI: 46.10–55.78) for tubercular meningitis, and 39.60 ± 7.065 mg/dl (95% CI: 37.72–41.56) for viral meningitis. This difference between CSF CPK is statistically significant between all groups [Tables 3 and 4].

DISCUSSION

The mean CSF LDH are 280.94 ± 74.488 mg/dl (95% CI: 261.60–300.48) for pyogenic meningitis, 171.24 ± 211.58 mg/dl (95% CI: 171.24–211.58) for tubercular meningitis, and 35.60 ± 10.394 mg/dl (95% CI: 32.58–38.36) for viral meningitis. This difference between CSF LDH is statistically significant between all groups.

In this study, the mean CSF CPK are 88.76 ± 15.083mg/dl (95% CI: 84.66–93.08) for pyogenic meningitis, 50.94 ± 18.716 mg/dl (95% CI: 46.10–55.78) for tubercular meningitis, and 39.60 ± 7.065 mg/dl (95% CI: 37.72–41.56) for viral meningitis. This difference between CSF and CPK is statistically significant between all groups.

A study by Dash and Patro showed mean LDH 271.4 ± 80.07 mg/dl for pyogenic meningitis and 199.71 ± 74.16 mg/dl for tubercular meningitis.[6]

Vekaria *et al*.[7] also showed in their study that CSF LDH level increase maximally in pyogenic meningitis with a range of 35.5–750 u/l and mean 171.25u/l, mild increase LDH activity in viral meningitis (17–75 u/l, mean 35.6 u/l), and moderately increases in tubercular meningitis (20.4–315 u/l, mean 105.65 u/l).[8]

Table 1: CSF and LDH among the study groups

Group	*n*	Mean±SD	95% CI
Pyogenic	50	280.94±74.488	261.60–300.48
Tubercular	50	192.14±76.018	171.24–211.58
Viral	50	35.60±10.394	32.58–38.36

CSF: Cerebrospinal fluid, LDH: Lactate dehydrogenase, SD: Standard deviation, CI: Confidence interval

Table 2: Comparison of CSF and LDH among the study groups

Groups	*P* value	Significance
Pyogenic versus tubercular	<0.0001	S
Tubercular versus viral	<0.0001	S
Viral versus pyogenic	<0.0001	S

CSF: Cerebrospinal fluid, LDH: Lactate dehydrogenase

Table 3: CSF and CPK among the study groups

Group	*n*	Mean±SD	95% CI
Pyogenic	50	88.76±15.083	84.66–93.08
Tubercular	50	50.94±18.716	46.10–55.78
Viral	50	39.60±7.065	37.72–41.56

CSF: Cerebrospinal fluid, CPK: Creatine phosphokinase, SD: Standard deviation, CI: Confidence interval

Table 4: Comparison of CSF and CPK among the study groups

Groups	*P* value	Significance
Pyogenic versus tubercular	<0.0001	S
Tubercular versus viral	0.0001	S
Viral versus pyogenic	<0.0001	S

CSF: Cerebrospinal fluid, CPK: Creatine phosphokinase

Another study carried out by Knight *et al.* showed that LDH activity is increased in CSF in pyogenic meningitis (mean 805, 95% CI 88–2452) as compared to control (reference range 0–24).[8]

Sharma and Nand showed that LDH level is significantly elevated in meningitis, the rise is more in pyogenic meningitis (260 ± 110.96) than in tubercular meningitis (190.48 ± 65.49) as compared to control (20.64 ± 3.63).[9]

The finding for CSF CPK is in accordance with studies conducted by Dash and Patro in which CPK is significantly elevated in pyogenic meningitis (87.17 ± 16.46) and tubercular meningitis (51.81 ± 19.9).[6]

Another study conducted by Sharma and Nand showed that CPK is elevated in meningitis, the rise is more in pyogenic meningitis (24.59 ± 14.51) than in tubercular meningitis (19.49 ± 9.17) as compared to control (5.18 ± 3.51).[9]

Another study which was published in International Journal of Advanced Research (2013) carried out by Afshan Zeeshan Wasti *et al*. showed that significantly increase CSF enzymatic activity in viral meningitis (LDH 32.8 ± 16.6, CPK42.0 ± 3.36) as compared to control (LDH 7.9 ± 3.05, CPK 15.2 ± 2.57).[10]

A study conducted in Tirkit University, in 2007, showed that mean level of CPK in patients with meningitis (20.99 ± 4.2) is higher than the control groups (5 ± 2.5), and the mean level of CPK in bacterial meningitis is higher than viral type, which is similar to that shown by Pancewicz.[11,12]

Limitations

1. Hospital-based study.
2. Small sample size.
3. Long-term follow-up was not done.
4. No control group.
5. For diagnosis of the different kinds of meningitis, the gold standard could not be followed in all cases due to technical difficulties.

CONCLUSION

Meningitis is a major life-threatening epidemiological problem, especially in developing countries like India. An early prompt diagnosis, efficient decision-making, and rapid institution of appropriate therapy can be lifesaving in a case of meningitis and, hence, are of utmost importance. In the present study, it was found that the enzymatic activity such as lactate dehydrogenase and creatine kinase was significantly elevated in CSF in cases of pyogenic meningitis and tubercular meningitis as compared to viral meningitis. Thus, CSF LDH, and CPK can serve as a useful marker to differentiate these three types of meningitis.

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