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ORIGINAL RESEARCH

Diagnostic Value of Lactate Dehydrogenase in CSF in Different Etiology of Meningitis

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ABSTRACT:
Background: Meningitis is an acute inflammation of the protective membranes, the brain and spinal cord, collectively known as the meninges. It is the most common sequelae to microbial invasion of the CNS. **Aim**: To study the diagnostic value of lactate dehydrogenase levels in CSF in different etiology of meningitis. Material and methods: The study included fifty patients (n=50) of meningitis, on the basis of clinical findings, CSF findings and MRI brain from cases admitted in emergency, indoor medical wards and ICU of Guru Nanak Dev Hospital, Amritsar. The CSF specimens were obtained by lumbar puncture using all the aseptic precautions. The following procedures were performed on all CSF specimens: Protein, Glucose, Analysis for total and differential leucocyte count and Gram stain, and culture on blood agar and heated blood agar. Chest X-ray, and ultrasound abdomen were done, when indicated. CSF LDH was recorded by kinetic method. **Results**: Mean age of subjects in our study came to be 41.6±17.1 years with male predominance. Mean LDH levels in TBM were 153.97±34.46 IU/L, in PM 238.25±32.06 IU/dl and in viral meningitis were 46.71±11.96 IU/L. On comparison the results were statistically significant. Overall, elevated LDH levels show 88% sensitivity. **Conclusion**: CSF LDH is markedly raised in pyogenic meningitis, moderately increased in tubercular meningitis and marginally increased in viral meningitis and the difference between the values is statistically significant. Hence CSF LDH may be sensitive biochemical markers for diagnosing and differentiating pyogenic, tubercular and viral meningitis.
Key words: meningitis, cerebrospinal fluid, LDH

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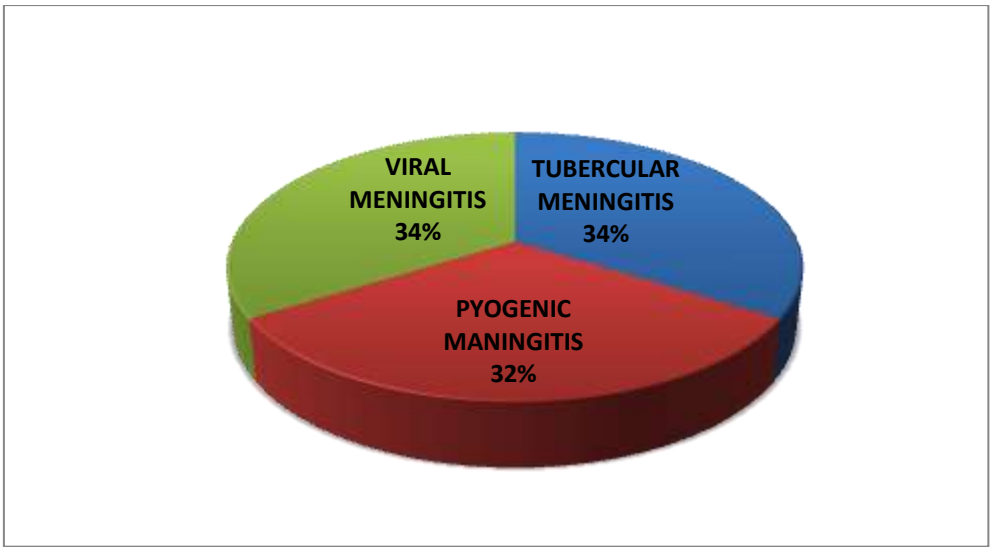
INTRODUCTION:
Meningitis is an acute inflammation of the protective membranes (pia and arachnoid mater) covering the brain and spinal cord, collectively known as the meninges.[1] It is more common in the developing countries than developed countries and is the most common sequelae to microbial invasion of the CNS. Neurological sequalae are serious and rather common among survivors.[2] The early diagnosis and treatment remains a challenge to the clinician.
The most common symptoms are fever, headache, vomiting and neck stiffness.[3] Other symptoms include confusion or altered consciousness and an inability to tolerate light or loud noise.[4] The classic triad of diagnostic signs consists of nuchal rigidity, sudden high fever, and altered mental status; however, all the three features are present in only 44–46% of bacterial meningitis cases.[4,5] Acute Meningitis is extremely unlikely, if none of the three signs are present.[4]
The information yielded by examination of Cerebrospinal fluid is often of crucial importance in the diagnosis of neurological disease.[6] Infectious meningitis is broadly classified into acute pyogenic (usually bacterial meningitis) aseptic (usually acute viral meningitis) and chronic usually (tuberculous, spirochetal or cryptococcal).
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. Various biochemical markers including Lactate dehydrogenase (LDH) have

been studied in diverse neurological conditions including different types of meningitis[7-9].
The CSF LDH is around 1/10th of the serum LDH level. Usual source is from the pia and arachnoid cells. Lactate dehydrogenase is an enzyme present in a wide variety of organisms including plants and animals.
Although many studies have acknowledged the CSF LDH levels in either diagnosis or prognosis of bacterial meningitis patients,[10-12] recent studies suggest that absence or low levels of CSF LDH (especially after 12 hours manifestation of clinical symptoms) strongly rule out bacterial meningitis.[13] CSF LDH value will not be altered with a short period of antibiotic therapy. It needs complete eradication of microorganisms. This is prognostically very significant. Hence LDH levels in CSF could prove to be a better predictor of bacterial meningitis besides other biochemical markers in CSF.
Therefore the present study was undertaken to study the diagnostic value of lactate dehydrogenase in CSF in different etiology of meningitis.

MATERIAL AND METHODS:
This hospital based cross-sectional study was conducted in the Department of Medicine, Guru Nanak Dev medical college and Hospital, Amritsar. The study included fifty patients (n=50) of meningitis, on the basis of clinical findings, CSF findings and MRI brain, cases admitted in emergency, indoor medical wards, and ICU of Guru Nanak Dev Hospital, Amritsar. This study was undertaken after approval of the Institutional Ethics Committee, Government Medical College, Amritsar. A Written informed consent of the patients was obtained in vernacular language for their inclusion. All those Patients who were diagnosed with meningitis and meningo-encephalitis were included in the study. While Patients of meningitis less than 14 years of age, with CVA/ stroke, with cirrhotic encephalopathy, those with uremic encephalopathy, with hypoxic ischemic encephalopathy and toxic-metabolic encephalopathy were excluded from our study.
The CSF specimens were obtained by lumbar puncture using all the aseptic precautions; The following procedures were routinely performed on all CSF specimens: Protein (Pennock, Passant, and Bolton, 1968)[14], Glucose (Glucose Analyser), Analysis for total and differential leucocyte count and Gram stain, and culture on blood agar and heated blood agar. Chest X-ray, and ultrasound abdomen were done, when indicated.
Complete clinical examination and proper detailed history of all the meningitis patients admitted in medical wards was recorded, at the time of admission. Finally, the clinical evaluation was observed and recorded. According to the above mentioned criteria patients were diagnosed as Tuberculous, Pyogenic and Viral Meningitis.
CSF LDH (by kinetic method[15]) is based on the principle that Lactate dehydrogenase catalyzes the reduction of pyruvate with NADH to for NAD. The rate of oxidation of NADH to NAD is measured as a decrease in absorbance which is proportional to the LDH activity in the sample. A Reference value in CSF [16] as 5-40 U/L at 37°C was considered as normal.

RESULTS:
Out of total 50 patients were included in our study, Mean age of subjects in our study came out to be 41.6±17.1 years with male predominance and Male: female ratio observed was of 1.63:1.
In the present study a total of 50 cases were studied among which 17cases (34%) were tubercular meningitis, 16 cases (32%) were pyogenic meningitis and 17 cases (34%) were viral meningitis. (Graph 1)

GRAPH 1: TYPES OF MENINGITIS ACCORDING TO DIAGNOSIS OF PATIENTS



In Tubercular meningitis (TBM) group, maximum patients (41.1%) were in the age group of 21-30 , in pyogenic meningitis (PM) group majority patients (31.2%) were in the age range of 31-40 years of age and in viral meningitis (VM) group, majority of cases (23.5%) were in the age range of 21-30 years and 51-60 years each.

Mean Hb levels in TBM group was 11±1.65 mg/dl, in PM group was 10.48±1.60 mg/dl and in VM group was 11.04±1.48 mg/dl While mean blood TLC levels in TBM group were 7604.7±1910.7 cells /cumm, in PM group was 8537.5±3248.97 cells /cumm and in VM group was 7282.35±1520 cells /cumm. These difference in results were not statistically significant.

Further, mean CSF cell count observed In TBM group was 59.23±42.62 cells/cumm, mean polymorphs 16.35±17.21%, mean lymphocytes 87.05±11.21%, the mean protein 154.11±43.36 mg/dl and the mean sugar 55.58±29.77 mg/dl. In pyogenic meningitis group, the mean CSF cell count was 242.87±339.50 cells/cumm, the mean polymorphs 80.13±67.05%, and the mean lymphocytes 28.37±19.2%, the mean protein 196.62± 42.1 mg/dl and the mean sugar 42.68±8.87mg/dl. Lastly in viral meningitis group, the mean CSF cell count was 14.29±4.07cells/cumm, the mean polymorphs of 28.13±20.12%, the mean lymphocytes of 71.47±12.14%, the mean protein 100.08±38.31mg/dl & the mean sugar of 88.17±20.13mg/dl.

On comparison, difference in values of all these parameters in three different types of meningitis was found to be statistically significant.

In the present study, LDH levels were found to be elevated (LDH >40 IU/dl) in 100% cases in TBM and 100% cases of pyogenic meningitis, while in viral meningitis only 64.7% cases presented with elevated LDH levels.(Table:1) Hence elevated LDH levels showed 100% sensitivity in TBM and PM group while in VM it was 64.7% sensitive. Overall, we reported elevated LDH levels in 44 out of 50 cases and thus 88% sensitivity of LDH is seen in our study.

TABLE 1: NUMBER OF CASES SHOWING ELEVATED LDH LEVELS IN DIFFERENT TYPES OF MENINGITIS

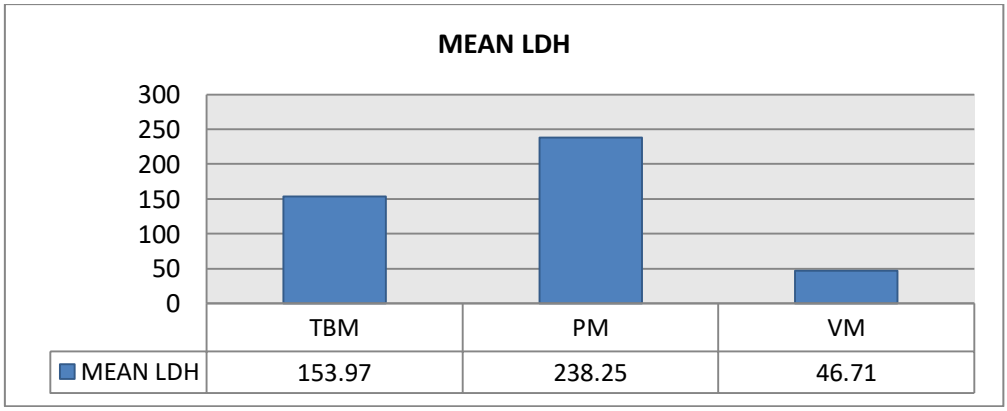
CSF ANALYSIS LDH LEVELS (IU/dl)	TBM (N=17)		PM (N=16)		VM (N=17)	
	N	%	n	%	n	%
ELEVATED (>40 IU/dl)	17	100%	16	100%	11	64.7%
NORMAL	0	0	0	0	6	35.2%

Observed LDH levels in TBM were in the range of 82-207 (IU/L) with mean of 153.97±34.46 IU/L, In pyogenic meningitis were 145-288 (IU/L) with mean of 238.25±32.06 IU/dl and in viral meningitis were36-87.2 (IU/L) with mean of 46.71±11.96 IU/L. On comparison, CSF LDH was markedly raised in pyogenic meningitis and moderately increased in TBM and the difference between the values in both the groups was statistically significant ($p<0.0001$, 95% CI= 60.6095 to 107.9505). Also, CSF LDH was marginally increased in viral meningitis and difference in its values from both TBM and PM was also statistically significant. ($p<0.001$, 95% CI= -125.2804 to -89.2396) (Table 2, Graph 2).

TABLE 2: CSF LDH LEVELS AND DIAGNOSIS IN DIFFERENT TYPES OF MENINGITIS.

DIAGNOSIS	TOTAL NO OF PATIENTS	LDH LEVELS (IU/L)		P VALUE
		MIN-MAX	MEAN	
TBM	17	82-207	153.97±34.46 IU/L	P<0.001*
PM	16	145-288	238.25±32.06 IU/L	
VM	17	36-87.2	46.71±11.96 IU/L	

GRAPH 2: MEAN CSF LDH LEVELS IN DIFFERENT TYPES OF MENINGITIS IN PRESENT STUDY



DISCUSSION:

Meningitis is a common health hazard and cause of hospitalization of considerable number of patients. It is a serious disease and may lead to significant morbidity and mortality. Those who survive may be left disabled. The early diagnosis and appropriate treatment definitely influences the outcome of this disease.

In our study, a total sample of fifty patients of meningitis were included. The mean age of subjects in our study came to be 41.6±17.1 years with male predominance. Based on cause of meningitis we divided our study subjects as, 17 cases (34%) of tubercular meningitis, 16 cases (32%) of pyogenic meningitis and 17 cases (34%) of viral meningitis.

Among Tubercular meningitis (TBM) group, 41.1% cases were in the age group of 21-30 years, in pyogenic meningitis (PM) group, 31.2% were in the age range of 31-40 years of age. While in viral meningitis (VM) group, 23.5% were in the age range of 21-30 years and 51-60 years each. Dash PC et al [17] reported that the mean age of patient was 35.43 years in case of TBM and 39.5 years in case of pyogenic meningitis. Also in yet another study conducted by Sharma et al [18] the mean age of patient was 35.12 years. This variation in age ranges can be explained on the basis that age varies as per locality and the category of patients admitted to the hospital where study is being conducted.

Mean CSF cell count in TBM group was 59.23±42.62 cells/cumm, mean polymorphs 16.35±17.21%, mean lymphocytes 87.05±11.21%, the mean protein level was 154.11±43.36 mg/dl and the mean sugar was 55.58±29.77 mg/dl. Where as in pyogenic meningitis group, mean CSF cell count was 242.87±339.50 cells/cumm, mean polymorphs 80.13±67.05%, mean lymphocytes 28.37±19.2%, mean protein was 196.62± 42.1 mg/dl and the mean sugar 42.68±8.87mg/dl. In a study by Jain et al, [19] cell count for TBM group was between 2000-3000 cells/cumm and mean protein value was 163±134.2 mg/dl. In yet another study by Sharma et al.[18], Mean protein value was 469.6±251.5 mg/dl and mean sugar value was 16.9±8.17mg/dl.

Further in viral meningitis group mean TLC level was 7282.35±1520, mean cell count was 14.29±4.07cells/cumm, the mean polymorphs 28.13±20.12%, the mean lymphocytes 71.47±12.14%, mean protein was 100.08±38.31mg/dl & mean sugar was 88.17±20.13mg/dl. On comparison, difference in values of number of cells, polymorphs, lymphocytes, protein and sugar content in all three different types of meningitis was found to be statistically significant.

In the present study, LDH levels are found to be elevated (LDH >40 IU/dl) in 100% cases of TBM (17/17 cases) and 100% cases of pyogenic meningitis (16/16 cases), while in viral meningitis only 64.7% cases (11/17cases) presented with elevated LDH levels. This was similar to observation made by Dash PCet al[17], Kepa L et al.[20], Sharma et al.[18], and Anita SP et al[21] who also reported elevated LDH levels in Pyogenic Meningitis. In viral meningitis, CSF LDH showed only a mild elevation.

Further it was observed that LDH levels in pyogenic meningitis were 145-288 (IU/dl) with a mean of 238.25±32.06. These results showed that on comparison, CSF LDH is markedly raised in pyogenic meningitis and moderately increased in TBM and the difference between the values in both the groups is statistically significant. Our results were in accordance to authors like Dash PC et al[17], Vekaria PN et al[22] and P.V. Nelson[23] who also reported that LDH activity in CSF in PM was significantly higher than in TBM.

Also on comparison, CSF LDH was marginally increased in viral meningitis and difference in its values from both TBM and Pyogenic Meningitis was also statistically significant. Anita SP et al[21] also reported elevated LDH levels in PM and in viral meningitis, CSF LDH showed only a mild elevation.

On contrary, Nayak BS et al[24] reported that serum LDH may not be useful in differentiating viral from other meningitis. It may act as a corroborative evidence of meningitis. Other authors like Wroblewski F[25] and Khanna SK[26] also reported no significant difference between TBM and Pyogenic Meningitis because of overlapping results. Although they reported a significant increase in CSF LDH activity in TBM and Pyogenic Meningitis as compared to Viral Meningitis.

Straus S. et al[27] in a systematic review reported that CSF lactate level of 31.53 mg/dL or more was accurate for diagnosing bacterial meningitis whereas a CSF lactate level of less than 31.53 mg/dL makes the diagnosis of bacterial meningitis less likely.

The mechanism by which the activity of LDH is increased in meningitis is still a subject of speculation. Various authors have attributed the rise to altered blood-brain/ CSF-barrier, presence of microorganisms and pleocytosis in CSF. It has been suggested that the 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 permeability of the CNS leading to disruption of BBB resulting into exudation of plasma proteins including LDH along with circulating leukocytes into the spinal fluid.

Our results show that elevated LDH levels show 100% sensitivity in TBM and Pyogenic Meningitis group while in Viral Meningitis it is 64.7% sensitive. Overall, our results show 88% sensitivity of LDH is seen in the present study. Similarly, Vekaria PN et al[22] reported that Estimation of CSF-LDH activity shows more sensitive (82.5%) and specificity (87.5%) to differentiate pyogenic meningitis from non bacterial meningitis. CSF-LDH level has inverse relationship with meningitis and direct relationship with leucocytosis.

Thus, overall results of our study showed that CSF LDH is markedly raised in pyogenic meningitis,

moderately increased in tubercular meningitis and marginally increased in viral meningitis and the difference between the values is statistically significant. Hence, we can suggest that estimation of these enzymatic activities can be helpful in diagnosing and differentiating pyogenic, tubercular and viral meningitis.

CONCLUSION:

We conclude from our results that as Meningitis is a major life-threatening disease with significant morbidity and mortality, an early prompt diagnosis and rapid institution of appropriate therapy can be lifesaving. Hence estimation of various enzymatic activities like CSF LDH levels can be helpful in diagnosing and differentiating pyogenic, tubercular and viral meningitis. Hence, the present study concludes that CSF LDH may be sensitive biochemical markers for diagnosing and differentiating pyogenic, tubercular and viral meningitis.

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