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International Journal of Clinical Biochemistry and Research

Journal homepage: www.ipinnovative.com

Original Research Article

Adenosine deaminase and lactate dehydrogenase levels in serum and cerebrospinal fluid of patients with tuberculous meningitis

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ARTICLE INFO

Article history:
Received 13-09-2020
Accepted 23-09-2020
Available online 28-09-2020

Keywords:
Tuberculous meningitis
ADA
LDH in Serum and CSF

ABSTRACT

Meningitis is an active inflammatory condition of CNS. However prompt and precise aetiological diagnosis remains a challenge. Often a thorough CSF examination may not give a precise diagnosis.
There is considerable urgency in establishing correct diagnosis in patients with tuberculous meningitis because specific therapy is most effective when initiated early in course of illness, delay may cause irreversible brain damage.
Diagnosis often rests on circumstantial evidence such as history, typical CSF findings and other evidence for presence of tuberculosis such as acid fast bacilli in sputum, positive tuberculosis test and suspicious Chest x-ray. Under present study the role of enzymes such as adenosine deaminase and lactate dehydrogenase has been evaluated in diagnosis of tuberculous meningitis. Result of the study suggest that adenosine deaminase level in CSF and serum may be a useful parameter along with other routine estimations. The enzyme activity is high in disease such as tuberculosis where cellular mediated immunity is stimulated.
Estimation of lactate dehydrogenase levels may not be a specific parameter for tuberculous meningitis this requires further studies in patients of meningitis with different aetiological diagnosis.

1. Introduction

Tuberculosis is a chronic granulomatous disease caused by mycobacterium tuberculosis, usually affecting the lungs, but virtually any extra pulmonary organ can be involved.[1] Initial exposure to mycobacteria results in development of a cellular immune response that confers resistance and leads to hypersensitivity as determined by a positive result on the tuberculin skin test.[2]

Tuberculous meningitis is always secondary to tuberculosis elsewhere in the body and usually arises from the formation of a metastatic caseous lesions in the cerebral cortex or meninges that develop during the lympho-haematogenous disseminations of the primary infection. The focal lesion in the brain substance is called a rich's focus,[3] this initial lesion increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudate may infiltrate the corticomeningeal blood vessels, producing inflammation, obstruction and subsequent infarction of cerebral cortex. The exudate also interferes with the normal flow of CSF in and out of the ventricular system at the level of the basilar cistern leading to a communicating hydrocephalus, profound abnormalities in electrolyte metabolism, due to salt wasting or the syndrome of inappropriate antidiuretic hormone secretion, also contribute to the pathophysiology of tuberculous meningitis.

Tuberculous meningitis is more common in children between 0 to 4 years of age,[4] occasionally TB meningitis may occur many years after the primary infection when rupture of one or more of the subependymal tubercles discharges tubercle bacilli into the subarachnoid space.

Biochemical changes occuring in cerebrospinal fluid in TB meningitis are lymphocytic pleocytosis, decreased glucose concentration and the protein level is markedly high

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https://doi.org/10.18231/j.ijcbr.2020.088

secondary to hydrocephalus and spinal block.[3]

Adenosine deaminase is an enzyme of the purine salvage pathway. ADA is a predominant t- lymphocyte enzyme. The activity of the enzyme is correlated to the maturative stage of the t- lymohocyte than to their number. In view of the central role of macrophages in immune function the levels of ADA are increased in tuberculosis where there is increased accumulation of macrophages.[5]

Lactate dehydrogenase, is an oxidoreductase enzyme whose activity is necessary for the reversible reaction in which pyruvate and lactate are interconverted. LDH exists in five electrophoretic distinguishable forms known as isoenzymes. These are LDH-1 - -LDH-5. The highest activity of LDH enzyme is found in brain, erythrocyte, white blood cells, kidney etc. Cerebrospinal fluid lactate dehydrogenase activity is increased in pathologic states that permit blood and plasma to reach the spinal fluid since enzyme activity from plasma lactate dehydrogenase is atleast five times greater than that of spinal fluid.[6]

In bacterial meningitis the resulting granulocytosis can produce an elevation of LDH-4 and LDH-5 isoenzymes and viral meningitis causes lymphocytosis, which may create an elevation of LDH-1——LDH-3.[7]

2. Materials and Methods

The study was carried out in 20 adults between 20 – 40 years admitted to owaisi hosptal and research centre and Princess Esra hospital, Hyderabad for meningitis and was investigated for tuberculous focus in the body x-ray chest showed active tuberculous lesion and mantoux test was positive. Cerebrospinal fluid from such cases was obtained by lumbar puncture with aseptic precautions and was subjected to biochemical analysis. Enzyme analysis was done immediately or the sample was preserved at temperature 4°c and was estimated within 24 hours. Serum was also analysed for the enzymes.

Normal cerebrospinal fluid for Controls was obtained from patients for spinal anaesthesia admitted for surgery for hydrocele or hernia.

Enzymes analysed are adenosine deaminase and lactate dehydrogenase in both cerebrospinal fluid as well as serum.

1. Estimation of adenosine deaminase in serum and CSF was analysed by kinetic method on semi-autoanalyzer, erba-chem 7.
2. Estimation of lactate dehydrogenase in serum and CSF was analyzed by u-v – kinetic method on semi-autoanalyzer, erba-chem 7.
3. CSF samples were also analysed for sugar, protein and cell count.
4. CSF sugar: GOD/POD method [glucose oxidase peroxidase].
5. CSF protein: Sulphosalicylic acid method [end point] on semi-autoanalyzer, erba-chem 7 at 620 nm.
6. CSF total cell count : cells are counted in neubar's chamber microscopically.

3. Results

Statistical analysis for the collected data was done by applying analysis of variance [Anova] 't' test was used to compare the two groups which were significantly different. Differences between various groups were considered to be significant when 'p' <0.05.

The Table 1 gives the descripitive for serum ADA (units/litre) in the study group were as follows. The mean and SD for control group is 15.15 ± 5.33 and for tuberculous meningitis group is 37.5 ± 11.16. 't' test to denote groups significant from each other showed that when compared to control group, there was a significant increase in mean serum adenosine deaminase levels in tuberculous meningitis group, the difference being statistically significant at p< 0.05 levels.

The mean and SD for CSF adenosine deaminase levels for control group 5.65 ± 1.75 and for tuberculous meningitis is 15.63 ± 2.71 't' test to denote groups significant from each other showed that when compared to control group, there was a significant increase in mean adenosine deaminase levels in tuberculous meningitis group, the difference being statistically significant at p < 0.031 level.

The descriptive for serum LDH (IU / litre) in the study groups were as follows. The mean and SD for control group is 90.55 ± 24.63 and for tuberculous meningitis group is 193.1 ± 21.15. 't' test to denote groups significant from each other showed that when compared to control group, there was a significant increase in mean serum lactate dehydrogenase level in tuberculous meningitis group, the difference being statistically significant at p < 0.002 level.

The mean and SD for CSF lactate dehydrogenase levels for control group is 18.45 ± 9.37 and for tuberculous meningitis group is 114.45 ± 47.58 't ' test to denote groups significant from each other showed that when compared to control group, there was a significant increase in mean cerebrospinal fluid LDH in tuberculous meningitis group, the difference being statistically significant at p < 0.01 level.

The descriptive for CSF cell count in the study groups were as follows. The mean and SD for control group is 1.5 ± 1.3 and for tuberculous meningitis 138.5 ± 73.64. 't' test to denote groups significant from each other showed that when compared to control group, there was a significant increase in mean cell count of CSF in tuberculous meningitis group, the difference being statistically significant at p < 0.07.

The mean and SD for CSF sugar levels for control group 53.35 ± 9.79 and for tuberculous meningitis group 34.15 ± 7.07. 't' test to denote groups significant from each other showed that when compared to control group, there was a significant decrease in mean CSF sugar in tuberculous meningitis group, the difference being statistically significant at p < 0.07 level.

The mean and SD for CSF protein values in study groups were as follows control group 31.2 ± 5.88 and for tuberculous meningitis group is 137.4 ± 51.21 ‘t’ test to denote groups significant from each other showed that when compared to control group, there was a significant increase in mean protein values of CSF in tuberculous meningitis group, the difference being statistically significant at $p < 0.02$ level.

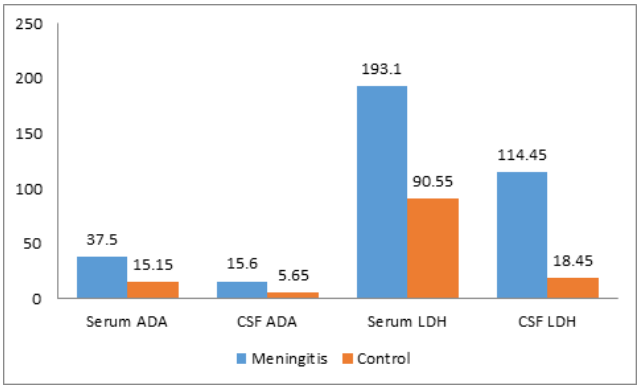

Fig. 1:

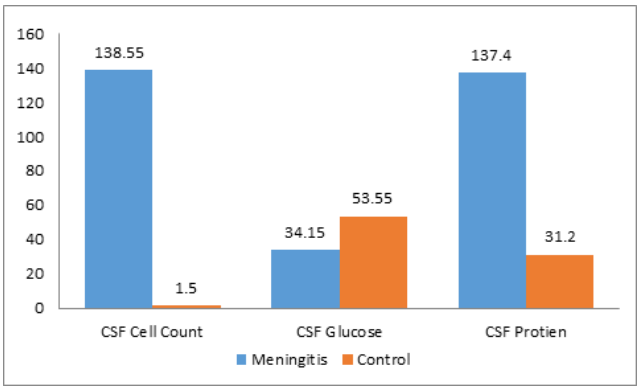

Fig. 2:

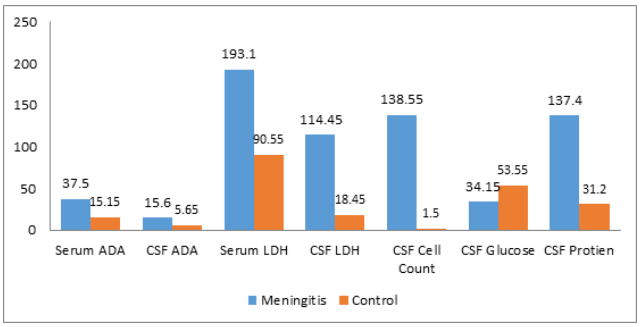

Fig. 3:

4. Discussion

Tuberculous meningitis, chronic bacterial infection remains undiagnosed in the initial stages and there is considerable urgency in establishing the correct diagnosis in patients with tuberculous meningitis, because specific therapy is most effective when instituted early in the cause of the illness.

Symptoms are highly variable and laboratory findings may not confirm the so called typical symptoms. In addition the microscopic demonstration of tubercle bacilli in CSF may be possible in only 10-20% of cases.[8]

Lumbar puncture with CSF examination usually reveals a clear fluid containing an increased amount of protein, a reduced level of glucose and an increased number of white blood cells with a predominance of lymphocytes.

However these findings alone can not confirm the diagnosis of tuberculous meningitis, since similar findings may be present in other types of bacterial meningitis, viral meningitis and viral encephalitis.

Serum adenosine deaminase levels in patients with tuberculous meningitis was 37.5 ± 11.6 units/100ml, these were significantly higher ($p < 0.05$) than normal controls in whom the enzyme levels were 15.5 ± 5.33 units/100ml.

CSF, adenosine deaminase levels in patients with tuberculous meningitis was 15.6 ± 2.71 units/100ml. while in normal subjects it was 5.65 ± 1.75 units/ 100ml. The enzyme levels are significantly raised in CSF of patients with tuberculous meningitis- although the enzyme levels in CSF are still lower than serum enzyme levels.

Adenosine deaminase is widely distributed through out mammalian tissues including cerebral cortex the lymphoid tissue has a particularly high enzyme level, the enzyme is produced to a greater extent by more differentiated activated lymphocytes the activity of enzyme is correlated to mature stage of t- lymphocytes, the activity is thus high in disease where cellular immunity is stimulated such as tuberculosis. In view of central role of macrophages in immune function, the levels of adenosine deaminase are increased in tuberculosis where there is increased accumulation of macrophages. A good cell mediated immune response is dependent on normal lymphocyte metabolism which is in part regulated by purine salvage enzymes and adenosine deaminase.[9]

Many factors have been suggested to play a role such as increased permeability of blood brain barrier due to pathological process and meningeal inflammation.Adenosine deaminase does not cross normal blood brain barrier. Damage to blood brain barrier may cause adenosine deaminase to enter cerebrospinal fluid.[10] Alternatively, raised CSF Adenosine deaminase may originate in local immune response as the result of lymphocyte proliferating in response to relevant antigen,the raised adenosine deaminase activity under antigenic stimulation shows its importance in rapid proliferation of cells in order to prevent the accumulation of toxic agents

Table 1:

Parameter	Control (MEAN ± SD)	Tuberculous meningitis (MEAN ± SD)	't'-value	'p'-value
Serum ADA	15.15 ± 5.33	37.5 ± 11.16	15.025	0.0534
CSF ADA	5.65 ± 1.75	15.63 ± 2.71	25.749	0.031
Serum LDH	90.55 ± 24.63	193.1 ± 21.15	40.829	0.0022
CSF LDH	18.45 ± 9.37	114.45 ± 47.58	10.756	0.01608
CSF Total Cell Count	1.5 ± 1.3	138.55 ± 73.64	8.4133	0.07869
CSF Polymorphs (%)	1.5 ± 1.3	21.25 ± 16.97		
CSF Lymphocytes(%)	1.5 ± 1.3	79.25 ± 16.53		
CSF Glucose (mg/dl)	53.55 ± 9.79	34.15 ± 7.07	21.592	0.07878
CSF Total Proteins(mg/dl)	31.2± 5.88	137.4 ± 51.24	11.998	0.02597

and thus reflects good cell mediated immunity.[11]

Serum Lactate dehydrogenase level in patients with tuberculous meningitis were 193.1 ± 21.15 units /100 ml these were significantly higher than the normal values of 90.55 ± 24.63 units/100 ml in control group ($p < 0.05$).

CSF, Lactate dehydrogenase levels in patients with tuberculous meningitis group was 114.45 ± 47.58 units/100ml these were significantly higher than the normal values of 18.45 ± 9.37 units/100 ml in control group (< 0.01).

The cell count was higher in cerebrospinal fluid (CSF) of patients with tuberculous meningitis. The count being 138.55 ± 73.64 as compared to 1.5 ± 1.3 in normal CSF, the lymphocytes were predominant. In meningitis there is increased permeability of vascular supply to CNS resulting in infiltration of WBC into CSF which in pyogenic meningitis Leucocytes are predominant cells and in viral and tuberculous meningitis Lymphocytes are predominantly increased.

CSF Sugar in tuberculous meningitis was 34.15 ± 7.07 mg/dl. This was significantly lower than the normal control value of 53.35 ± 9.79 mg/dl. Normal CSF glucose is considered to be greater than 45 mg/dl. Active metabolism of glucose by cells or organisms due to infection usually reduces CSF glucose levels. Decreased transport has also been suggested to be contributory factor in TB meningitis.

Total protein in CSF of patients with TB meningitis was 137.4 ± 51.21 mg/dl. This was significantly higher than the levels in normal CSF which was 31.2 ± 5.88 mg/dl. Increased total protein in CSF may occur due to increased permeability of epithelial membranes due to bacterial infection or an obstructive process or adhesions causing decrease in rate of removal.

Result of the study suggest that apart from estimation of usual parameters in CSF such as cell count, protein and sugar levels which may not be sufficient in confirming diagnosis of tuberculous meningitis. Estimation of adenosine deaminase levels may be a useful parameter in confirming the diagnosis.

Lactate dehydrogenase activity may be a less specific parameter than adenosine deaminase activity whether CSF Lactate dehydrogenase activity is of any diagnostic significance is still a matter of controversy.

5. Conclusion

The enzymes estimated are adenosine deaminase and lactate dehydrogenase in cerebrospinal fluid and serum are significant in tuberculous meningitis patients compared to the normal individuals. Where as estimation of lactate dehydrogenase levels may not be a specific parameter for tuberculous meningitis this requires further studies in patients of meningitis with different aetiological diagnosis. The analysis of cerebrospinal fluid Total cell count, glucose and proteins are significant in tuberculous meningitis patients compared to normal subjects according to the study done.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Jalees SS, Hussain ST. Adenosine deaminase and lactate dehydrogenase levels in serum and cerebrospinal fluid of patients with tuberculous meningitis. *Int J Clin Biochem Res* 2020;7(3):411-415.