

Cerebrospinal fluid Transaminases as discriminatory marker in meningitis

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*Article History:

Received: 11/04/2018

Revised: 21/04/2018

Accepted: 21/04/2018

DOI: <https://doi.org/10.7439/ijbar.v9i4.4741>

Abstract

Back ground: Bacterial meningitis (BM) is a life-threatening disease with high mortality rates and bad neurologic sequelae; however, it is a potentially treatable disease, whereas aseptic (viral) meningitis (AM) mostly subsides spontaneously. Therefore, BM represents a medical emergency.

Objective: To study cerebrospinal fluid Transaminases and other marker in meningitis.

Material and Methods: The present study was carried out in the Department of Biochemistry at Government Medical College and Hospital, Aurangabad during the period June 1999 to June 2001 on 40 patients of meningitis and 20 controls from pediatric age group. CSF and blood samples from patients suffering from pyogenic meningitis (32) (Group II), tuberculous meningitis (Group III) (8) and control subjects (Group I) (20) were examined. Statistical analysis was done by One way ANOVA non-parametric test with Tukey-test to compare all the group was used and calculated by SPSS 19 version of the software.

Result: In our study we have seen that CSF sugar was Significantly lower in the Pyogenic Meningitis Group (II) as compared to Controls (I) and Tuberculous meningitis (III) group ($p < 0.05$) and also CSF/Blood Sugar Ratio was significantly lower Pyogenic (II) and Tuberculous (III) Meningitis group as compared to Control (I) ($p < 0.05$). CSF Proteins were significantly higher in Pyogenic (II) and Tuberculous Meningitis group (III) as compared to controls ($p < 0.05$). CSF GPT was significantly higher in Pyogenic (II) and Tuberculous (III) meningitis as compared to control (I).

Conclusion: CSF GOT was significantly increased in pyogenic meningitis as compared to tuberculous meningitis. Thus we have concluded that CSF GOT, GPT help the clinician for diagnosing meningitis in addition to the routine investigations. Further CSF GOT may help in the differentiation between pyogenic and tuberculous meningitis.

Keywords: Meningitis, Pyogenic meningitis, Tuberculous meningitis, Transaminases, CSF GOT, CSF GPT.

1. Introduction

Bacterial meningitis (BM) is a life-threatening disease with high mortality rates and bad neurologic sequelae [1,2]; however, it is a potentially treatable disease, whereas aseptic (viral) meningitis (AM) mostly subsides spontaneously. Therefore, BM represents a medical emergency [3] and early antibacterial therapy is essential for a good outcome.

Normal glucose concentration in the CSF is 50-80 mg% [4]. Glucose concentration in the Cerebrospinal fluid (CSF) is commonly measured in patients suspected of having bacterial meningitis, since it is usually decreased as

a result of bacterial metabolism. If the CSF is frankly purulent, the measurement of CSF glucose provides no usual additional information.

The CSF glucose concentration is approximately 65% of the blood glucose concentration and CSF glucose should always be interpreted in the light of the glucose concentration of a blood sample obtained at the same time [5].

The CSF glucose is generally believed to be half to two thirds of blood glucose when these are estimated simultaneously [6].

1.1 Proteins in CSF:

Protein concentration in the CSF is normally 15-45 mg% [4] and the protein is predominantly albumin. In meningitis there is secretion of IgG into the CSF but this has little effect on the total amount of protein. However meningeal inflammation may lead to an increase in capillary permeability and therefore a marked increase in CSF protein content. It is important to note that in suspected meningitis, normal CSF protein does not exclude the meningitis [5]. CSF Criteria for bacterial meningitis:

- 1) Elevated CSF proteins usually 100-500 mg% (normal 20-45 mg%),
- 2) Reduced CSF glucose < 40 mg% [Normally > 50 mg%, 75% of blood glucose].
- 3) CSF leukocytosis significantly polymorphonuclear leukocytes (100-60,000 mm³) (normally < 5 mm³, 75% lymphocytes).
- 4) Definite bacteria on stained smear and/or culture.
- 5) Normal or elevated CSF pressure (Normal 50-80 mm H₂O) [7].

CSF is the hallmark of the tuberculous meningitis. There is history of contact or evidence of Koch's in the patient, a positive Mantoux and elevated proteins, decreased sugar, lymphocytosis and acid fast bacilli or Zeihl Neelsen stain positive in the CSF.

Majority of cases of meningitis can often be diagnosed with clinical examination; there remains a definite group of patients in whom initial diagnosis is often in doubt because of overlapping symptoms and signs.

Levels of CSF biochemical constituents like proteins, glucose, chloride, globulin together with cellular components are routinely examined for diagnosis. However it is not certain whether this data provides sufficient confirmation to the diagnosis which results in undue delay in the initiation of appropriate therapy. The quest for newer methods for arriving a precise diagnosis therefore continues.

Diagnostic considerations in the sphere of neurologic diseases are usually derived from history and physical findings with limited guidance afforded by laboratory procedures. In recent years the investigations and interpretation of changes in serum enzymes has been one of the most rapidly expanding fields in clinical biochemistry. Estimation of the serum levels of enzymes is a helpful investigation in diagnosis of hepatic, myocardial, muscular and neoplastic diseases. Presently these tests are being utilized in diagnosing neurological disorders like meningitis. The applied tests are estimation of transaminases [glutamic oxaloacetic transaminase (GOT) & glutamic pyruvic transaminase (GPT)] and lactate dehydrogenase (LDH) in cerebrospinal fluid.

1.2 Transaminases (GOT, GPT):

Transaminases (GOT & GPT are the enzymes which transfer amino group from one amino acid to a

ketoacid and lactate dehydrogenase is an oxidoreductase which reversibly catalyse the conversion of lactate to pyruvate [8].

1.3 Biological significance of Transaminases (GOT & GPT) and LDH: Transaminases:

Transaminases were first demonstrated in animal tissue by Braunstein and Kritzman in 1937 [9]. Pyridoxal phosphate is the prosthetic group of transaminases acting as an amino group carrier.

By the process of transamination living organisms are able to convert pyruvic acid a product of carbohydrate metabolism into alanine. Thus body is able to synthesize new amino acids by utilizing ketoacids which are the byproduct of carbohydrate and fat metabolism.

The process of transamination is also important from the point of oxidation - reduction systems involved in Kreb's cycle, where non nitrogenous compounds like pyruvic acid, a ketoglutaric acid and oxaloacetic acid take part. It then appears that transamination may be shuttle mechanism in which a few key protein and carbohydrate metabolism are interconverted as needed.

GOT and GPT are widely distributed in the tissues. Myocardium has highest quantity of GOT followed by liver, skeletal muscle and kidney. GPT is found in large amount in liver followed by kidney, heart and skeletal muscle. Central nervous tissue contains more GOT than hepatic tissue and almost as much as cardiac muscle [10,11].

2. Patients and Method

The present study was carried out in the Department of Biochemistry at Government Medical College and Hospital, Aurangabad during the period June 1999 to June 2001.

The study was carried out on 40 patients of meningitis and 20 controls from pediatric age group. The diagnosis of meningitis was made on clinical findings, microscopic examination of CSF, biochemical examination of CSF, culture studies and radiological studies.

Twenty patients whose final diagnosis was primarily non neurological for example respiratory tract infections gastroenteritis septicemia etc. were selected as controls.

Fourty patients of meningitis included 32 suffering from pyogenic meningitis and 8 suffering from tuberculous meningitis.

CSF and blood samples from patients suffering from pyogenic meningitis (32), tuberculous meningitis (8) and control subjects (20) were examined. Estimation of Blood Glucose was done by Trinders Methods) Estimation of CSF glucose: method is same as Blood Glucose but instead of plasma CSF sample is used Estimation of CSF total proteins by turbidometric method [8].

Estimation of CSF GOT and CSF GPT were done by the method of Reitman and Frankel [8].

Table 1: Showing number of cases and their groups

Group	Study Subject	Case
I	Controls	20
II	Pyogenic meningitis	32
III	Tuberculous meningitis	08
	Meningitis (Total)	40

Over all the Controls were 20 (Group I), Pyogenic meningitis were 32 (Group II), and Tuberculous meningitis were 08 (Group III) and Total meningitis patients were 40.

2.2 Statistical analysis

Statistical analysis was done by One way ANOVA non-parametric test with tukey-test to compare all the group was used and calculated by SPSS 19 version of the software.

3. Result

Table 2: Comparison of biochemical parameters in meningitis

Parameters	Controls (n=20) I	Meningitis (total) (n=40)	Pyogenic Meningitis (n=32) II	Tuberculous meningitis (n=8) III
BSL (mg%)				
Range	75-118	58-150	58-150	67-131
Mean±S.D.	91.7± 12.86	88.82±22.85	88.71±23.16	89.25±23.64
CSF sugar (mg%)				
Range	58-80	12-45	12-45	19-43
Mean± S.D.	64.4±5.42	26.62±7.2*	25.37±7.06*	31.62±9.08**
CSF/Blood Sugar Ratio				
Range	0.56-0.8	0.129-0.43	0.129-0.4	0.28-0.43
Mean± S.D.	0.7±0.06	0.3±0.06*	0.29±0.6*	0.35±0.05**
CSF Proteins (mg%)				
Range	18-40	60-560	60-560	95-274
Mean± S.D.	27.25±7.23	145.5±89.02**	141.87±94.40**	160±66.26**
CSF GOT (IU/L)				
Range	7-11	9-24	9-24	9-19
Mean± S.D.	9.1±1.88	15.8±3.46**	16.43±3.22**	13.25±3.41**
CSF GPT (IU/L)				
Range	5-11	7-24	7-24	7-17
Mean± S.D.	7.3±1.97	13.05±3.44**	13.25±3.5**	12.12±3.22**

*p value =<0.001; ** P-value =<0.05; * and ** statistically significant

From above Table it is clear that CSF sugar was Significantly lower in the Pyogenic Meningitis Group (II) as compared to Controls (I) and Tuberculous meningitis (III) group (p<0.05)

From above table it is clear that CSF/Blood Sugar Ratio was significantly lower Pyogenic (II) and Tuberculous (III) Meningitis group as compared to Control (I) (p<0.05) but were comparable to each other in the group (II and III) (p>0.05)

From above Table it is clear that CSF Proteins were significantly higher in Pyogenic (II) and Tuberculous Meningitis group (III) as compared to controls (p<0.05) but comparable with each other (II vs III) (p>0.05)

It is clear that CSF GOT was significantly higher in Pyogenic meningitis (II) as compared to Control (I) and Tuberculous meningitis (III) (p<0.05).

It is clear that CSF GPT was significantly higher in Pyogenic (II) and Tuberculous (III) meningitis as compared to control (I) i.e. p<0.05, but comparable to each other (II vs III) p>0.05.

4. Discussion

In our study we have seen that CSF sugar was Significantly lower in the Pyogenic Meningitis Group (II) as compared to Controls (I) and Tuberculous meningitis (III) group (p<0.05) and also CSF/Blood Sugar Ratio was significantly lower Pyogenic (II) and Tuberculous (III) Meningitis group as compared to Control (I) (p<0.05) but were comparable to each other in the group (II and III) (p>0.05).

Behera *et al* [12], done estimation of CSF sugar, blood sugar and CSF/blood sugar ratio in 50 cases each of pyogenic (age 1 month-9 years) and tuberculous meningitis (age 8 month-11 years) in fasting state by Nelson's Somogyi method. In pyogenic group 38 cases (recovered) mean CSF and blood sugar values were 23.7±5.35 mg% and 92.85±11.58 mg% respectively and their mean ratio was 0.25±0.05 and in 12 cases (fatal) mean CSF and blood glucose levels were 6.33±6.62 mg% and 93.66±18.47 mg% respectively and their mean ratio was 0.076±0.29. In tuberculous group 34 cases (recovered) mean CSF and

blood sugar values were 31.33 ± 5.54 mg% and 92.6 ± 11.42 mg% respectively and their mean ratio was 0.34 ± 0.051 and in 16 cases (fatal) mean CSF and blood glucose levels were 25.6 ± 4.56 mg% and 91 ± 8.2 mg% respectively and their mean ratio was 0.274 ± 0.05 . In both types of meningitis mean CSF sugar and CSF/blood sugar ratio was significantly lowered compared to normal value and CSF sugar and CSF/blood sugar ratio was significantly low ($P < 0.001$) in pyogenic meningitis than in tuberculous meningitis. Blood sugar level was maintained more or less to the same value as compared to normal. It has been proposed that low CSF sugar is due to synergistic effect of glycolysis by bacteria and leucocytes. There is increased permeability of membrane in meningitis for which we get increased protein content in the CSF but glucose transport is not by simple diffusion method. So the glucose transport mechanism has been postulated to be mainly due to damage to the specific mechanism in the cell membrane that can readily transfer glucose molecules despite their insolubility in lipids (carrier facilitated diffusion).

CSF Proteins were significantly higher in Pyogenic (II) and Tuberculous Meningitis group (III) as compared to controls ($p < 0.05$) but comparable with each other (II vs III) ($p > 0.05$). Chakravorti B.P. (1969), studied protein bound carbohydrates and electrophoretogram of CSF proteins in controls (10 cases), tuberculous meningitis (10 cases). Total CSF protein was determined by Meulemansturbidometric method. Mean value of CSF protein in controls was 30 ± 3.16 mg% and tuberculous meningitis was 75 ± 15 mg%. The level of total protein in CSF of children with tuberculous meningitis was more than normal.

CSF GOT was significantly higher in Pyogenic meningitis (II) as compared to Control (I) and Tuberculous meningitis (III) ($p < 0.05$). CSF GPT was significantly higher in Pyogenic (II) and Tuberculous (III) meningitis as compared to control (I) i.e. $p < 0.05$, but comparable to each other (II vs III) $p > 0.05$.

Mansour *et al* [13], studied levels of individual serum and CSF protein in purulent meningitis (27 cases) and in tuberculous meningitis (28 cases) and in controls (9 cases). Mean CSF protein level in control group was 209 mg/lit (20.9 level of 24 units or more was associated with complications in 30 of 38 patients. In a laboratory measure of prognosis the CSF GOT value probably represented a more specific but less sensitive measure when compared with the CSF glucose or CSF protein level. In acute purulent meningitis the elevated CSF GOT activity may be attributed to changes in CSF blood brain barrier, damage to brain tissue or to presence of white blood cells (WBCs) or bacteria or to a combination of these factors.

Srivastava G[14] estimated the level of transaminases in the CSF in 40 cases of various neurological disorders and in 20 controls.

The estimation of transaminase was done by colorimetric method. In controls CSF GOT levels ranged from 2-14 units/ml with a mean of 8.65 units/ml. He observed in cases of tuberculous meningitis CSF levels of GOT were 5-120 units/ml with a mean of 32.58 units/ml. 65% of cases had values above the normal range. The rise of transaminase levels in the CSF has been partly explained by the alteration of the haemocephalic barrier due to the inflammatory process which permits increased passage of serum proteins and especially the globulin fraction.

Mellick *et al* [11], reported raised levels of GOT in CSF might be for the following reasons.

- 1) An increased outflow from serum through incompetent CSF/blood brain barrier to this enzyme.
- 2) An increased out flow from cells is because of their destruction.
- 3) An increased outflow from cells in the absence of their destruction.
- 4) Decreased rate of removal.
- 5) Combination of some or all the factors.

Srivastava G [14], reported increased CSF GPT in tuberculous meningitis and mean was 32.58 units as compared to 8.65 units in control. In tuberculous meningitis 65% of the cases had CSF transaminases values above the normal range. The rise of transaminase levels in the CSF has been partly explained by the alteration of the haemocephalic barrier due to the inflammatory process which permits increased passage of serum proteins and especially the globulin fraction with which these enzymes are associated in the CSF. It can be postulated that the rise in enzymatic content may be due to the increased cellular content of CSF since leucocytes have a high endogenous enzymatic content. It is likely that the transaminases might have been liberated into the CSF from the cells of the affected brain tissue following the inflammatory process and thus higher levels of transaminases in the CSF may reflect a greater brain damage.

5. Conclusion

Blood sugar maintained more or less to the same value in pyogenic meningitis, tuberculous meningitis and controls. CSF proteins of pyogenic as well as tuberculous meningitis were significantly increased as compared to controls. CSF GOT, GPT were significantly increased in pyogenic and tuberculous meningitis as compared to controls. CSF GOT was significantly increased in pyogenic meningitis as compared to tuberculous meningitis. Thus we have concluded that CSF GOT, GPT help the clinician for diagnosing meningitis in addition to the routine investigations. Further CSF GOT may help in the differentiation between pyogenic and tuberculous meningitis

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