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Role of Cerebrospinal fluid Lactate Dehydrogenase in meningitis

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Abstract

Background: Meningitis still remains a condition of significant mortality and morbidity in pediatric practice. Tubercular and bacterial meningitis form an important group of neurological diseases associated with considerable mortality and morbidity in children.

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) ($p<0.05$) but were comparable to each other in the group (II and III) ($p>0.05$). 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) ($p>0.05$). In present study: Mean CSF LDH value of meningitis (total) was significantly increased ($P<0.05$) as compared to controls. Mean CSF LDH value in meningitis (total) was 87.42±28 IU/L as compared to 26.85±10.79 IU/L in controls.

Conclusion: We have concluded that LDH help the clinician for diagnosing meningitis in addition to the routine investigations, further LDH may help in the differentiation between pyogenic and tuberculous meningitis.

Keywords: CSF LDH, Pyogenic meningitis, Tubercular meningitis, Biochemical markers of meningitis.

1. Introduction

Meningitis still remains a condition of significant mortality and morbidity in pediatric practice. Tubercular and bacterial meningitis form an important group of neurological diseases associated with considerable mortality and morbidity in children.

Bacterial meningitis is a fatal disease if untreated. With availability of modern antibacterial agents, mortality has been substantially reduced but is associated with significant morbidity in the form of serious neurological and mental sequelae like psychomotor retardation, deafness, and seizures. A late diagnosis and inadequate chemotherapy increases the incidence of these crippling sequelae.

Incidence of mortality is clearly related to the late initiation of the treatment. A late or missed diagnosis of tubercular meningitis can have serious consequences and diagnosis is far from easy.

1.1 Definitions

The dura mater is a pachymeninx the inflammation of which is termed as pachymeningitis but this term is rarely used. The pia and arachnoid mater are called leptomeninges. The inflammation of which is called leptomeningitis now, reduced to meningitis [1].

1.2 Meningitis

It is an inflammation of the leptomeninges and cerebrospinal fluid (CSF) by infectious or non infectious processes. The most common infectious agents are: Bacterial, tubercular, viral, protozoal and fungal. The non-infectious agents are malignancy, subarachnoid hemorrhage and sarcoidosis [2].

1.3 Meningismus

It is the presence of signs of meningeal inflammation in the absence of meningitis [1].

1.4 Acute bacterial meningitis

It is defined as an inflammation in response to bacterial infection of the pia, arachnoid and the fluid residing in the space as it encloses and also the fluid in the ventricles of the brain.

Since subarachnoid space is continuous space around the brain, the spinal cord and optic nerves, meningitis is always cerebrospinal [3].

Bacterial meningitis is caused by bacterial agents like Streptococcus pneumoniae, *Escherichia coli, Hemophilus influenzae*, Neisseria mening/t/cf/s etc.

Accurate and rapid diagnosis of acute bacterial meningitis (BM) is essential because disease outcome depends on immediate initiation of appropriate antibiotic therapy [4]. BM should be treated promptly with antibiotics, whereas acute aseptic meningitis (AM) is usually self limiting. However, differentiating BM from AM may be challenging for clinicians because the symptoms and laboratory assays are often similar and overlapping. In addition, classical clinical manifestations of BM in infants and children are usually difficult to recognize because of the absence of signs of meningeal irritation and because of delayed elevation of intracranial pressure. Parameters examined in cerebrospinal fluid (CSF) are less descriptive in children than in adults: in enterovirus meningitis, CSF parameters can be practically identical to those of bacterial meningitis. For example, acute meningitis with predominance of neutrophils in CSF suggests BM; however, herpes simplex-1 infected meningitis presents with > 90% neutrophils in CSF [5]. Furthermore, other assays, such as Gram stain, latex agglutination, and polymerase chain reaction-based assays, lack sensitivity [6-9]. In practice, before definitive CSF bacterial cultures are available, most patients with acute meningitis are treated with broadspectrum antibiotics targeting BM. In general, this does not seriously harm the AM patient; however, it may enhance the local frequency of antibiotic resistance [10] and cause antibiotic adverse effects, nosocomial infections [11], and high medical costs [12]. Thus, it is not only important to recognize BM patients who promptly need antimicrobial therapy but also AM patients who do not need antibiotics and/or hospital stays.

In recent years, it has been proposed that CSF lactate may be a good marker that can differentiate bacterial meningitis (> 6 mmol/l), from partially treated meningitis (4 to 6 mmol/l) and aseptic meningitis (< 2 mmol/l) [13]. However, other researchers have suggested that CSF lactate offers no additional clinically useful information over conventional CSF markers [14,15].

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 [16], Colorimetric Method was used For Estimation of CSF Lactate Dehydrogenase (LDH) [16].

2.1 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 1: Age and sex distribution in controls (n=20)

Age group	Male	Female	Total
0-11 month	1(5%)	1(5%)	2(10%)
1-4 yrs.	4(20%)	4(20%)	8(40%)
5-9 yrs.	2(10%)	2(10%)	4(20%)
10-12 yrs.	5(25%)	1(5%)	6(30%)
Total	12(60%)	8(40%)	20(100%)

As shown in table 1 in controls male to female ratio was 1:5:1 and maximum numbers of children were in the age group of 1-4 yrs (40%).

Table 2: Age and sex distribution in meningitis (n=40)

Age group	Male	Female	Total
0-11 month	12(30%)	2(5%)	14(35%)
1-4 yrs.	12(30%)	5(12.5%)	17(42.5%)
5-9 yrs.	3(7.5%)	1(2.5%)	4(10%)
10-12 yrs.	3(7.5%)	2(5%)	5(12.5%)
Total	30(75%)	10(25%)	40(100%)

As shown in Table 2, in meningitis group 75% were males and 25% were females. Maximum numbers of children were below the age group of 5 yr (77.5%).

Table 3: Age and sex distribution in pyogenic meningitis (n=40)

Age group	Male	Female	Total
0-11 month	11(34.38%)	2(6.25%)	13(40.62%)
1-4 yrs.	8(25%)	5(15.62%)	13(40.62%)
5-9 yrs.	2(6.25%)	1(3.12%)	3(9.37%)
10-12 yrs.	2(6.25%)	1(3.12%)	3(9.37%)
Total	23(71.88%)	9(28.12%)	32(100%)

As shown in Table 3, in pyogenic meningitis group 71.87% were males and 28.125% were females and 13 cases (40.625%) were below the age of 1year

Table 4: Age and sex distribution in Tuberculous meningitis (n=40)

Age group	Male	Female	Total
0-11 month	1(12.5%)	--	1(12.5%)
1-4 yrs.	4(50.0%)	--	04 (50.0%)
5-9 yrs.	1(12.5%)	--	1(12.5%)
10-12 yrs.	1(12.5%)	1(12.5%)	2(25.0%)
Total	7(87.5%)	1(12.5%)	8(100.0%)

As shown in Table 4, in tuberculous meningitis group 87.5% were males and 12.5% were females. 62.5% were below the age group of 5 years.

Table 5: 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.

Table 6: 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±7.8	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 LDH (IU/L)				
Range	5-44	49-180	50-180	49-119
Mean ± S.D.	26.85±10.79	87.42±28	91.84±27.91	69.75±21.76

Table 7: Distribution of the patients as per the patients as per CSF sugar in different meningitis group (One way ANOVA)

ANOVA Table	SS	df	MS		
Treatment (between columns)	19250	2	9623		
Residual (within columns)	2635	57	46.23		
Total	21880	59			
Tukey's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
I vs II	39.03	28.48	Yes	***	34.36 to 43.69
I vs III	32.53	16.17	Yes	***	25.68 to 39.37
II vs III	-6.500	3.420	Yes	*	-12.97 to -0.02803

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 ($p<0.05$)

Table 8: Distribution of the patients as per the patients as per CSF/Blood Sugar Ratio in different meningitis group (One way ANOVA)

ANOVA Table	SS	df	MS		
Treatment (between columns)	1.592	2	0.7962		
Residual (within columns)	0.9653	57	0.01694		
Total	2.558	59			
Tukey's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
I vs II	0.3555	13.55	Yes	***	0.2662 to 0.4448
I vs III	0.2918	7.579	Yes	***	0.1607 to 0.4228
II vs III	-0.06375	1.753	No	ns	-0.1876 to 0.06012

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) ($p>0.05$)

Table 9: Distribution of the patients as per the patients as per CSF Proteins in different meningitis group (One way ANOVA)

ANOVA Table	SS	df	MS		
Treatment (between columns)	190500	2	95270		
Residual (within columns)	309300	57	5426		
Total	499900	59			
Tukey's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
I vs II	-114.8	7.730	Yes	***	-165.3 to -64.21
I vs III	-134.7	6.179	Yes	***	-208.9 to -60.44
II vs III	-19.88	0.9653	No	ns	-89.99 to 50.24

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) ($p>0.05$)

Table 10: Distribution of the patients as per the patients as per CSF LDH in different meningitis group (One way ANOVA)

ANOVA Table	SS	df	MS		
Treatment (between columns)	51920	2	25960		
Residual (within columns)	29580	57	519.0		
Total	81500	59			
Tukey's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
I vs II	-64.91	14.14	Yes	***	-80.55 to -49.28
I vs III	-42.85	6.359	Yes	***	-65.80 to -19.90
II vs III	22.06	3.465	Yes	*	0.3788 to 43.75

From above Table it is clear that CSF LDH level was significantly higher in pyogenic meningitis group (II) as compared to Control (I) and Tuberculous meningitis group (III) ($p<0.05$)

4. Discussion

The measurement of CSF lactate concentration is a simple, rapid, inexpensive assay, takes just 15 minutes, and can be performed at the bedside. In addition, the CSF lactate concentration is useful during the course of treatment, because a rapid CSF lactate decrease is indicative of good prognosis [17]. Since the CSF lactate concentration is not specific for BM, the results of this assay should be interpreted in parallel with clinical findings and the results of conventional assays including CSF concentrations of protein, cells, glucose, and a microbiological examination of CSF. The cut-off value for CSF lactate concentration ranges from 2.1 to 4.44 mmol/L, suggesting a variance between instrument, hospital labs, and the method. Therefore, every center should set its own cut-off value for CSF lactate concentration. Another disadvantage of CSF lactate is that it is not useful in the choice of antibiotic selection, which must be based on the results of microscopic examination of a smear or culture for bacteria, as well as the other clinical data. The mechanism of the increased concentration of lactate in the CSF of patients with BM is not clear, but it has been linked with anaerobic glycolysis of brain tissue due to a decrease cerebral blood flow and oxygen uptake [18,19].

Additionally, the concentration of CSF lactate is independent of serum lactate, probably due to its ionized state that crosses the blood-CSF barrier at a very slow rate [20], suggesting another advantage over CSF glucose assay [21].

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) ($p>0.05$)

Reddi *et al* [22], conducted a study of CSF to blood sugar ratio in 100 normal children and 50 each of pyogenic meningitis, tuberculous meningitis. Blood and CSF glucose was measured by Folin Wu method. Normal blood sugar levels ranged from 60 to 115 mg%, the mean blood sugar value being 87.5 mg%. The corresponding CSF sugar levels varied from 45-80 mg% with mean value being 52.5 mg%. CSF sugar to blood sugar ratio ranged from 0.55 to 0.75 mean ratio being 0.63. In pyogenic meningitis blood sugar levels ranged from 60 to 116 mg%, and corresponding CSF sugar levels ranged from 10 to 35 mg%. The ratio ranged from 0.2 to 0.38 mean being 0.24 and in tuberculous meningitis blood sugar values ranged from 65-115 mg%, while corresponding CSF sugar values ranged from 20 to 45 mg%. The ratio thus ranged from 0.22-0.45 mean ratio being 0.35. Damage to carrier mediated transport and glycolytic activity of bacteria and leucocytes in synergism in CSF has been responsible for low CSF sugar and CSF/blood sugar ratio, studies had further indicated that CSF/blood sugar ratio may be lower in pyogenic than tubercular meningitis, lower ratio in pyogenic than tubercular meningitis may be due to that tuberculous meningitis is characterised by relatively dominant lymphocytic response as opposed to purulent meningitis which is characterised by polymorphonuclear response and it is known that lymphocytes take up glucose less avidly than polymorphs [23,24]

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 [25] studied protein bound carbohydrates and electrophoretogram of CSF proteins in controls (10 cases), tuberculous meningitis (10 cases). Total CSF protein was determined by Meulemans turbidometric 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.

In present study: Mean CSF LDH value of meningitis (total) was significantly increased ($P<0.05$) as compared to controls. Mean CSF LDH value in meningitis (total) was 87.42±28 IU/L as compared to 26.85±10.79 IU/L in controls.

Mean CSF LDH value of pyogenic meningitis was significantly increased (PO.05) as compared to controls. Mean CSF LDH value in pyogenic meningitis was 91.84±27.91 IU/L as compared to 26.85±10.79 IU/L in controls.

Mean CSF LDH value of tuberculous meningitis was significantly increased (PO.05) as compared to controls. Mean CSF LDH value in tuberculous meningitis was 69.25±21.76 IU/L as compared to 26.85±10.79 IU/L in controls.

Mean CSF LDH value of pyogenic meningitis was significantly increased ($P<0.05$) as compared to tuberculous meningitis. Mean CSF LDH value in pyogenic meningitis was 91.84±27.91 IU/L as compared to 69.25±21.76 IU/L in tuberculous meningitis.

4.1 Our study is supported by

Gupta *et al* [26] estimated LDH activity in serum and CSF in 100 patients with neurological disorders and 20 control cases between the ages of 1 month and 12 years. The LDH was estimated by colorimetric method. The normal CSF LDH value was 25.96 IU/L with a range from 3-47 IU/L. A definite increase in LDH activity in CSF was observed in cases of acute bacterial meningitis mean 97.8±43.7 IIJ/L with a range from 35.28-18 IU/L and in tuberculous meningitis was mean 65.98±22.6 IU/L with a range from 22.8-114 IU/L. Increased levels of CSF LDH were in pyogenic meningitis and tuberculous meningitis as compared to controls (PO.Ol). The increase was more marked in the former (four times the normal mean) than the later. Initial mean enzyme level in CSF in patients with pyogenic meningitis who expired was very high (mean 114.54±43.07) as compared to those who recovered completely (mean 66.58±13.68) and this rise was statistically significant however in cases of tuberculous meningitis the increase in LDH value in patients who expired was statistically insignificant.

5. Conclusion

It can be concluded from our study that CSF sugar and CSF/blood sugar ratio was decreased significantly in meningitis; both pyogenic and tuberculous meningitis as compare to controls. 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 significant increased as compared to controls.

LDH were significantly increased in pyogenic and tuberculous meningitis as compared to controls and LDH was significantly increased in pyogenic meningitis as compared to tuberculous meningitis.

Thus we have concluded that LDH help the clinician for diagnosing meningitis in addition to the routine

investigations, further LDH may help in the differentiation between pyogenic and tuberculous meningitis.

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