CEREBROSPINAL DEHYDROGENASES IN CENTRAL NERVOUS SYSTEM INFECTIONS

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ABSTRACT

Cerebrospinal fluid (CSF) dehydrogenases were studied in 42 controls, 23 children with pyogenic meningitis, 22 with tuberculous meningitis and 19 with encephalitis to assess their usefulness in differentiating between the different central nervous system infections.

CSF-LDH and ICD activity was increased in CNS infections ($p < 0.0001$), LDH being significantly higher ($p < 0.001$) in pyogenic meningitis than in tuberculous meningitis or encephalitis. However, ICD activity was significantly different in each of these conditions ($p < 0.001$). The dehydrogenase activity declined with subsequent clinical improvement, in all children with meningitis.

A significant direct relationship was found between the enzyme activity and CSF protein content as well as total cell count.

The 95% confidence interval confirms the utility of assaying CSF dehydrogenase activity to differentiate various CNS infections, thus improving the diagnostic ability.

Key words: *CSF-LDH, CSF-ICD, Pyogenic meningitis, Tuberculous meningitis, Encephalitis.*

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Accumulation of lactic acid in cerebrospinal fluid (CSF) as a result of a large number of WBCs has been reported by Aslam *et al.*(1) in meningitis who thought enzyme estimation is a cumbersome procedure. The estimation of enzyme activity in the CSF can be used for the diagnosis of various central nervous system (CNS) disorders. The dehydrogenase enzymes are present in various body tissues. Various workers(2-6) have demonstrated that CSF lactate dehydrogenase (LDH) and isocitrate dehydrogenase (ICD) activities are increased in CNS infection but only a few workers(7-8) have studied these enzymes simultaneously in pyogenic meningitis (PM); tuberculous meningitis (TBM) and encephalitis. This study was, therefore, undertaken to determine if the assay of enzyme activity helps to differentiate these infections so as to improve the diagnostic ability in complicated cases of CNS infection.

Material and Methods

Cerebrospinal fluid dehydrogenase activity was studied in 106 children. Their ages ranged from 6 months to 12 years. Mean age was 5.14 years in 42 controls who had convulsive disorders, with normal cerebrospinal fluid and no neurological deficit. Each case was subjected to detailed history, clinical examination, Mantoux test, *X*-ray chest and skull and CSF examination. Sonography of skull and CT scan of brain was performed wherever possible.

The diagnosis of pyogenic and tuberculous meningitis was made from routine clinical and CSF examination. Patients were diagnosed as acute encephalitis on the basis of (*a*) CSF mononuclear pleocytosis, (*b*) normal CSF sugar, (*c*) normal or slightly raised protein, and (*d*) favorable

clinical responses without use of antibiotic therapy.

Pyogenic meningitis was diagnosed on the basis of (*a*) CSF leucocytosis with ≥ 90% polymorphs, (*b*) very low sugar, (*c*) moderate increase in protein, and (*d*) favorable response to antibiotics. Tuberculous meningitis (TBM) was considered if CSF showed (*a*) leucocytosis with ≥80% lymphocytes, (*b*) increase in protein, (*c*) normal or slight reduction in sugar, and (*d*) evidence of tuberculous pathology and/or positive family history as supportive evidence. Patients in whom there was any dilemma about diagnosis have been excluded from this study.

CSF-LDH and ICD enzyme activity was estimated by colorimetric method, described by King(9), and Bell and Baron(10) respectively.

CSF examination was repeated 3-5 days later in pyogenic meningitis and at discharge in both TBM and pyogenic meningitis.

Pearson's correlation coefficient was used to assess the relation of CSF protein and cells with CSF dehydrogenase. Students' paired 't' test was also used.

Results

The CSF-LDH and CSF-ICD activity increased in all cases of central nervous system infections ($p<0.0001$). It increased significantly in pyogenic meningitis (*Table I*) in comparison with TBM and encephalitis ($p<0.001$). The CSF-LDH does not differentiate between tuberculous meningitis and viral encephalitis. CSF-ICD, however, can differentiate these clinical conditions ($p<0.001$). The dehydrogenase enzyme activity declined in pyogenic meningitis in subsequent assays along with clinical improvement. It returned to normal within 10-14 days in pyogenic meningitis and by 4-6 weeks in TBM. The enzyme activity was plotted against CSF protein and total cell count (*Figs. 1 & 2*).

Table II shows that LDH and ICD activity correlated with rise in CSF protein and cell count in pyogenic meningitis and encephalitis, but this correlation was relatively poor in TBM. *Table III* mentions the 95% confidence interval for LDH and ICD in various clinical conditions.

Discussion

Lactate dehydrogenase (LDH) and isocitrate dehydrogenase (ICD) are normally present in the cerebrospinal fluid (CSF) and other body fluids including plasma. There is no correlation between serum and spinal fluid activity(1). Normal CSF-LDH and CSF-ICD activity in our study was 11.69 ± 3.98 and 10.74 ± 3.56 units/ml, respectively. These values are similar to those reported by some workers(2-5), while others(7,8,11) reported higher values of CSF-LDH. Rymenant*et al.*(6) reported 6-7 units/ml of CSF-ICD levels in normal spinal fluid.

The mechanism by which spinal fluid LDH activity increases is not clearly understood. It is suggested that pathologic states that permit blood and plasma to reach the spinal fluid result in increased values by virtue of contribution of enzyme activity from plasma LDH, which is five times higher than that of the spinal fluid(2). Meningeal inflammation compromises the blood brain barrier, resulting in the release of various components into CSF. Also, CNS infection with active phagocytosis and lysis of bacterial cells might result in the liberation of enzymes into CSF(3). It is, thus evident that CSF-enzyme activity will increase in inflammed meninges. It will

TABLE I--*Cerebrospinal Fluid Examination (Mean ±ID)*

Group	Cells (c/cu mm)	Protein (mg/dl)	LDH (units/ml)	ICD (units/ml)
1. Pyogenic meningitis (n=23)	2747.43 ±3115.79	163.65 ± 134.42	365.30 ±125.20	40.81 ± 5.92
	321.39 ± 9.59 †	78.91 ± 27.09	136.65 ± 57.99	18.99 ± 5.20
2. Tuberculous Meningitis (n=22)	434.55 ± 325.43	119.09 ± 79.73	39.36** ± 13.39	21.19 ± 5.53
3. Encephalitis (n=19)	6.95* ± 5.88	30.42 ± 20.27	47.63 ± 27.256	14.358 ± 3.86
4. Controls (n=42)	4.02 ± 3.40	14.476 ± 3.89	11.69 ± 3.98	10.74 ± 3.56

-- All values compared with controls $p < 0.0001$ except * $p < 0.05$

-- PM vs TBM $p < 0.001$
PM vs encephalitis $p < 0.001$
TBM vs encephalitis $p < 0.001$
except ** Not significant

– † Repeat CSF after 3-5 days $p < 0.001$.

TABLE II--*Correlation Coefficients (r)*

Parameter	Pyogenic meningitis (n = 23)		Tuberculous meningitis (n = 22)		Encephalitis (n = 19)	
	LDH	ICD	LDH	ICD	LDH	ICD
Protein	0.84*	0.732*	0.648**	0.558*	0.932*	0.593*
Cells	0.908*	0.806*	0.736*	0.595**	0.91*	0.737*

* $p < 0.001$, ** $p < 0.01$

TABLE III--*95% Confidence Interval for LDH and ICD in Various Conditions*

Condition	LDH (unit/ml)	ICD (unit/ml)
Pyogenic meningitis	320.47 – 410.13	38.69 – 42.93
Tuberculous meningitis	34.45 – 44.27	19.76 – 23.83
Encephalitis	34.53 – 57.57	12.82 – 15.89
Controls	10.66 – 12.72	9.82 – 11.66

* Mean value.

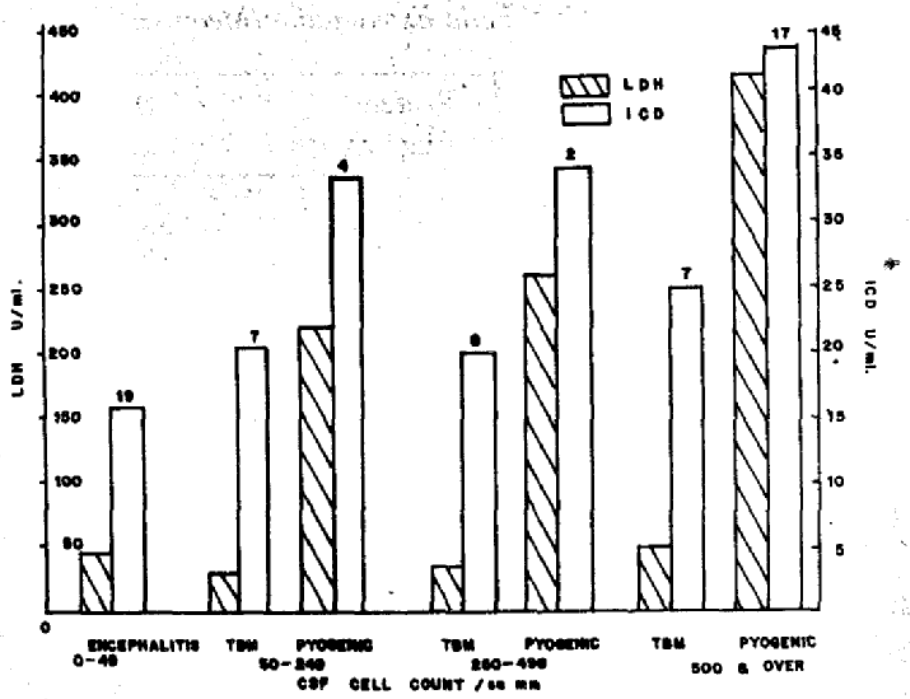

Fig. 1. Correlation of CSF cell count with enzyme activity

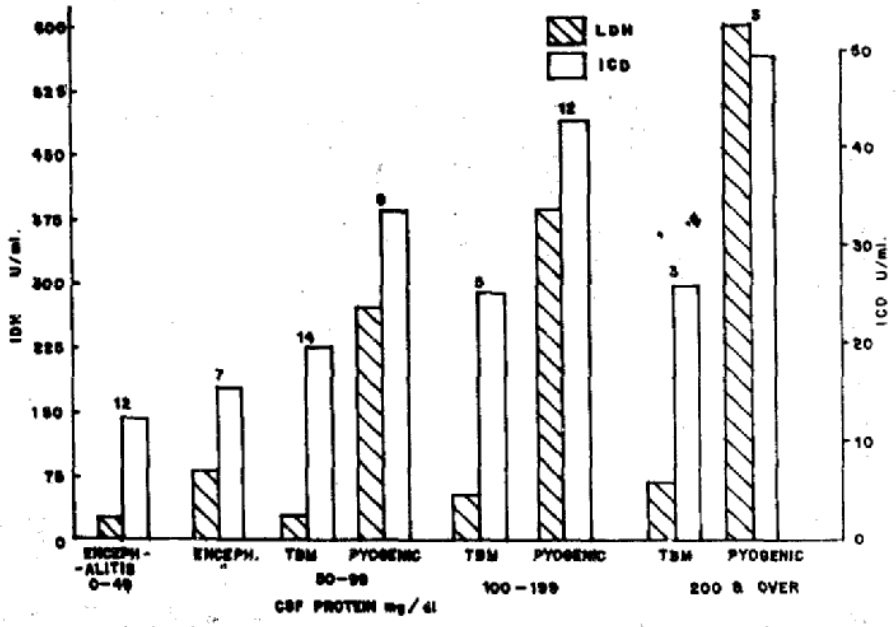

Fig. 2. Correlation of CSF protein with enzyme activity.

increase further if there is the element of phagocytosis and lysis of bacteria as can be seen in pyogenic meningitis.

CSF-LDH activity was ten times higher in PM than in encephalitis of viral origin in our study as well as of other workers. Rymenant *et al.*(6) observed similar trend of CSF-ICD activity in bacterial and viral meningitis, respectively. Children with convulsive disorder have little change in enzyme activity in comparison with the control(4). In a study on puppies by Lending *et al,* the increase in enzyme activity was only evident after prolonged seizures of at least

30 minutes duration and they thought increased cerebral cell membrane permeability was a major factor(12).

This finding is a useful diagnostic criterion in the early differentiation between viral and bacterial meningitis and also between pyogenic and tuberculous meningitis. This is unlike Davel *et al.* who did not find CSF-LDH assays helpful to differentiate between TBM and PM; infact he reported low CSF-LDH activity in PM(8). Some workers(7,8,14) reported higher CSF-LDH activity than ours; however, their control values were also higher than ours. The poor exudative response in spinal fluid is responsible for smaller rise of LDH activity in TBM in the present study as well as that of Agarwal *et al.*(5). The increase in CSF-LDH, however, does not differ significantly from LDH of viral encephalitis in the present study; while Agarwal *et al.* reported significant rise in TBM as compared to viral encephalitis(5). There was no change in LDH levels from control in viral encephalitis in their study. This could be due to encephalitis being considered as an exclusion diagnosis. The CSF-ICD activity did differentiate between encephalitis and TBM in our study ($p<0.001$).

The correlation between CSF-LDH and ICD, and CSF protein and total cell count was examined in TBM and PM patients. There was significant linear relationship between enzyme activity and protein and total cell count in both PM ($r=0.7 - 0.9$, $p<0.001$) and TBM ($r=0.5 - 0.7$, $p<0.01$). No significant difference was found in the slope of the regression lines. At any given level of protein and total cell count, PM has higher enzyme activity. The 95% confidence interval revealed a highly significant difference in the activity of LDH and ICD in both groups. The analysis of CNS infection has shown that dehydrogenase activity should be interpreted along with CSF protein, sugar and cell count and not in isolation. Subsequent enzyme assays in pyogenic meningitis during the course of disease reflected clinical response and in some cases have even preceded it. Patients who respond favorably to therapy have showed at least 60% decline in enzyme activity within 3-5 days. This can also help in borderline cases especially, when CSF findings are misleading or inconclusive and antibiotics may be inappropriate. In such situations, LDH and ICD activity in spinal fluid may be useful in critical evaluation of diagnosis.

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