DISCUSSION
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The use of enzymes as a diagnostic tool is not new. It was Kamen in 1935 who observed the serum glutamic oxaloacetic transaminase elevations in transmural myocardial infarction in man. The role of serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase in diseases of liver is another such example.

These changes are based on the fact that serum levels of enzymes rise whenever tissues abundant in them are damaged. That this property holds true for other body fluids also, has been a subject of much theoretical and practical attention. Long before this, Kaplan et al., (1936) had already focussed their minds on the enzymatic activities of the spinal fluid. Armed with the knowledge that damage to nervous tissue could cause elevations of enzyme levels in the spinal fluid, these workers studied various enzymes in normal and pathological spinal fluids. As time progressed interests changed from one disease to another. Interest in cerebrospinal fluid enzymology was heightened by Busher (1952) who found increased triosephosphate isomerase activity in cerebrospinal fluid in cerebrovascular accidents. The recognition of the fact that intracellular enzymes could be absent from blood stream after central nervous tissue injury was presumed to reflect the influence of a blood brain barrier (Fisher et al., 1957).
The normal range of glutamic oxalacetic transaminase and lactic dehydrogenase activity of cerebrospinal fluid obtained from persons without disease of the central nervous system has differed in various reports. These differences contribute to divergent interpretations of the changes of enzyme activity observed in pathologic states of the central nervous system (Wrblewski, 1953). Reports on the clinical significance of alterations in cerebrospinal fluid G.O.T. and L.D.H. activities also differ. Increases in these enzymes in C.S.F. are usually correlated with acute and significant injury to the central nervous system of diverse causes including those of thromboembolic, infections, degenerative and neoplastic origin. The increase in enzyme activity appears to occur at varying times after the onset of central nervous tissue injury. However, clinically significant central nervous tissue injury may occur without increased G.O.T. and L.D.H. activity. Correlation between serum and C.S.F. enzyme activities is yet to be firmly established. From the data presently available it would appear that a clear cut picture of role of C.S.F. enzymes in common neurological illnesses is yet to emerge.

In view of the present situation in this field, this study was planned to evaluate the importance of C.S.F. and serum levels of G.O.T. and L.D.H. in acute cerebrovascular episodes and encephalomyelitis. Stress was maintained on selecting only those cases who presented
within a certain specified time period after the onset of illness. This was done with a view to obviate the changes of a decline of enzyme activity after the destructive process induced rise in the enzyme levels. Diseases which could result in a documented rise in the enzymes being studied were excluded from the study group. Twenty patients with no disease likely to affect the levels of G.O.T. and L.D.H. served as controls.

SERUM GLUTAMIC OXALOACETIC TRANSMISASE AND LACTIC DEHYDROGENASE CHANGES IN CASES OF CEREBRAL INFARCTION AND INTRACRANIAL HEMORRHAGE:

(a) Glutamic oxaloacetic transaminase:

This enzyme was significantly raised in all cases of cerebrovascular accidents. Serum G.O.T. increments in cerebrovascular accidents have also been reported by Lieberman et al. (1957), Fleischer et al. (1957), Hyerson et al. (1957), Brodell et al. (1959), Mathur et al. (1966) and Singh et al. (1972). However the above findings are at variance with those of Giebert and Fleischer (1956), Green et al. (1957) and Leha and Bhargava (1964). These workers did not report any serum G.O.T. increment in cerebrovascular accidents. Leha and Bhargava attributed this to the presence of an intact blood brain barrier.

Peak serum G.O.T. levels were obtained between fourth and seventh day of the onset of illness. However, in cases of hemorrhage the enzyme levels showed maximum rise in first three days and declined thereafter. In both
groups however, the levels did not touch normal till the last follow up which was up to eleventh day in infarction and up to seventh day in haemorrhage. Lieberman et al. (1957) reported peak levels of serum G.O.T. between one to five days of onset of illness. In another series of 21 patients of recent cerebrovascular accidents, Lieberman et al. in the same year reported maximal serum G.O.T. elevations from second day to third day after onset of symptoms in majority of their patients. Brodell et al. (1959) recorded maximum activity between second to fourth day of illness. Nathur et al. (1966) reported peaks between second to fourth day of illness. However Singh et al. (1972) reported peak serum G.O.T. values within first five days of illness except in cerebral thrombosis where it was observed between sixth to tenth day of illness. Kaul et al. (1978) reported rising serum G.O.T. values in their cases of cerebral thrombosis with peak in second week of onset of illness. The diversity in the observations of various workers, regarding the time of peak enzyme activity can in part be explained by the fact that the time of examination of blood carries much importance. An elevated level of activity may return to normal if the estimation is done at a time remote from the time of attack.

The early peak observed in cases of cerebral haemorrhage is in consonance with the findings of Nathur et al. (1966) who also observed an early peak in cases of
haemorrhage in comparison to thrombosis or embolism. These observations however are at variance with those of Singh et al. (1972) and Kaul et al. (1978) who did not report early peak values in cases of haemorrhage as compared to cerebral thrombosis or embolism. An earlier peak in cases of haemorrhage may be due to the presence of blood in C.S.F., thereby contributing to the rise in enzyme level induced by parenchymal damage. In the present work the serum G.O.T. levels failed to touch the normal levels even on last follow up (which was between eighth to eleventh day in infarction cases and between fourth to seventh day in cases of haemorrhage) and were statistically significant in both groups ($P \leq 0.01$ and $\leq 0.001$ respectively). Similar findings have been reported by Singh et al. (1972) and Kaul et al (1978). However Mathur et al (1969) could record near normal values of serum G.O.T. by twelfth day in cases of cerebral thrombosis and eighth day in cases of cerebral embolism.

Serum G.O.T. levels in cerebral haemorrhage were found to be significantly higher in comparison to cases of cerebral infarction in the present work. This could be due to admixture of blood with C.S.F. However, no definite diagnostic cut off level could be found for serum G.O.T. in our series.

Similar have been the observations of Singh et al. (1972) and Kaul et al (1978). Lichtenman et al in 1957, however reported almost similar increments in serum G.O.T.
in cases with cerebral thrombosis and haemorrhage. Mathur et al. (1963) reported maximum serum G.O.T. elevation in cases of subarachnoid haemorrhage. Observation of rise in both C.S.F. and serum G.O.T. levels in the patients with cerebral infarction and haemorrhage may be due to disruption of blood brain barrier in acute cerebrovascular accidents. Mehlick and Bassett (1964) have suggested that cerebral hypoxia leading to damage to the capillaries with subsequent leak may be an important factor.

(b) Lactic Dehydrogenase:

In the present study serum L.D.H. remained within normal limits. This observation is in conformity with that of Haiek and Blumenthal (1956), Fleisher et al. (1957), Wolinty et al. (1969) and Bedi et al. (1974). However, the above findings are at variance with those of Lowenthal (1961) and Chaudhri et al. (1976). These workers reported increments in serum L.D.H. activity in cases of cerebrovascular accidents. Chaudhri et al. (1976) reported maximum levels in cerebral haemorrhage. All of their serum enzyme increments came back to normal by tenth day after registering a peak on fifth day. No definite plausible explanation for this lack of rise in serum L.D.H. seems possible. The impermeability of blood brain barrier to L.D.H., the molecular structure and weight of this enzyme and the extent of cerebral damage responsible for raised cerebrospinal fluid L.D.H. activity may interplay with each other to produce a final effect.
CEREBROSPINAL FLUID GLUTAMIC OXALOACETIC TRANSAMINASE
AND LACTIC DEHYDROGENASE LEVELS IN CASES WITH CEREBRAL
INFARCTION AND HEMORRHAGE:

(a) **Glutamic oxaloacetic transaminase:**

Significant elevations of cerebrospinal fluid G.O.T.
levels were observed in cases with cerebral infarction and
hemorrhage. The levels were found to be raised from the
time of admission and maintained this trend till the last
follow up which was between eighth to eleventh day in
cases of infarction and fourth to seventh day in cases of
hemorrhage. The peak values (15.5±6.6 I.U./L and 34.9±13.6
I.U./L respectively) in infarction and hemorrhage were
obtained on admission itself and the levels showed a
decline thereafter. When cerebral infarction was compared
to hemorrhage significant difference in the enzyme levels
of the two was found, the values in hemorrhage being desig-
dedly higher (P ≤ 0.001). In consonance with this finding
Flesher et al (1957) have reported moderate elevations of
transaminase activity in a study of cerebrovascular disease
in human beings. Lieberman et al (1957) found definite
G.O.T. transaminase elevations in 7 out of their 18
patients with cerebral infarction. Raised cerebrospinal
fluid G.O.T. values in cerebrovascular disease has been
reported by Green et al (1957, 56), Brdall et al (1956),
Hallick and Bassett (1964), Mathur et al (1963), Pradhan
and Samaa (1963), Rama Rau, S. (1963), Singh et al (1972)
Kohli et al (1978, 81) and Kaul et al (1978). However
Katzman (1957) and Myerson et al. (1957) did not find significant transaminase rise in C.S.F. in cases of cerebrovascular accidents.

Various workers have reported peak levels of different time intervals after the onset of stroke, in contrast to the peak reported within one to three days in the present study. Brodell et al (1959) reported peak values within two to four days of the onset of illness with large infarcts only. Significant elevations could only be found within a week after onset in cerebrospinal G.O.T. in the series reported by Mallick and Sassett (1964). In the series by Mathur et al. (1965), cerebrospinal fluid G.O.T. was elevated within 24 hours and reached its peak by second day. Pradhan and Saxena (1965) contended that significant rise of cerebrospinal fluid G.O.T. occurred in the C.S.F. samples collected before 16 hours after the onset of infarction. Singh et al. (1972) found peak activity within first five days. Peak activity on fifth day was also reported by Kohli et al. (1978). Kaul et al (1978) reported peak levels within a week in cases of haemorrhage and in second week in cases of cerebral infarction.

The diversity in enzyme values may be ascribed to the difference in clinical material. Slow extension of a thrombus over a period of some days may produce highest levels later on.
In the present series the enzyme levels did not touch normal till the last follow up which was between eighth to eleventh day in cases of infarction and between fourth to seventh day in cases of haemorrhage. Lieberman et al. (1957) could detect raised levels of C.S.F. enzymes in a case even on fifteenth day. Brodell et al. (1959), however, reported significant rise in serum and C.S.F. enzyme levels during the first ten days. Laha and Bhargava (1964) reported normal values by tenth day of the onset of illness. Mathur et al. (1965) found that the raised levels returned to normal by the twelfth day. Davies Jones (1970) reported normal values in his series of patients examined 5 weeks after the episode. Singh et al. (1972) observed a declining trend in the enzyme levels but the levels did not touch normal even after tenth day. Similar were the findings of Kohli et al. (1978). Kaul et al. (1978) reported high levels of cerebrospinal fluid C.O.T. persisting even up to third week after the onset.

Significantly higher values were obtained in cases of cerebral haemorrhage as compared to infarction. Similar findings have been reported by Singh et al. (1972) Kaul et al. (1978) and Kohli et al (1978). However, Mathur et al. (1965) reported highest enzyme values in cases of subarachnoid haemorrhage rather than cerebral haemorrhage.
Laha and Bhargava (1964) could not report any significant difference in the degree of rise of enzyme activity between various types of cerebrovascular accidents.

The higher C.S.F. G.O.T. values in cerebral haemorrhage could be due to more extensive cortical damage in cerebral haemorrhage than elsewhere. Admixture with blood may have further added to higher cerebrospinal fluid G.O.T. values.

(b) Lactic Dehydrogenase

In the present study cerebrospinal fluid L.D.H. levels were significantly elevated in both the groups of cerebrovascular disease, infarction as well as haemorrhage ($P \leq 0.001$). These findings are in conformity with those of Flaissher et al. (1957), Wroblewski et al. (1957), Jakoby and Jakoby (1958), Green et al. (1959), Wolints et al. (1969), Bedi et al. (1974), and Chaudhri et al. (1976). Wroblewski et al. (1958) on the other hand, reported normal cerebrospinal fluid L.D.H. levels in majority of cases of cerebral thrombosis. There was no correlation between C.S.F. and serum L.D.H. Similar findings have been reported by Wolints et al. (1959) and Bedi et al. (1974). The rise in cerebrospinal fluid L.D.H. levels in cases of cerebrovascular diseases may be due to the following factors:

1. Release of the enzyme from the infarcted tissue (or necrotic areas).
2. Release from the degraded extravasated blood in cases of haemorrhagic lesions.

Peak levels of cerebrospinal fluid L.D.H. were obtained within the first three days of the onset of illness in infarction as well as haemorrhage. Jakoby and Jakoby (1958) reported that levels may be low soon after symptoms appear and increase only after some days. Wroblewski et al (1958) reported maximum activity within one to three days. Similar were the findings of Walisz et al. (1969). In cases of cerebral haemorrhage the peak levels were obtained on first day by Chaudhri et al. (1976).

The differences in the time of peak enzyme activity may be accountable by the fact that the time of removal of C.S.F. may vary in each series. Also the extent of damage produced, too, may alter the results.

Cerebrospinal fluid L.D.H. levels were significantly higher (P < 0.001) till last follow up in cases of infarction as well as haemorrhage. Wroblewski (1958) reported that cerebrospinal fluid L.D.H. levels returned to normal by fifth to tenth day. Bedi et al (1974) reported that C.S.F. enzyme values came to normal after three weeks in patients who survived.

Comparatively extremely high cerebrospinal fluid L.D.H. levels were found in haemorrhage as compared to infarction (P < 0.001). This in conformity with findings of Wroblewski et al (1958) who reported similar
increments in cerebrospinal fluid L.D.H. in haemorrhage. Similar findings were reported by Wolints et al. (1969), Badi et al. (1974) and Chaudhri et al. (1976). Higher values of cerebrospinal fluid L.D.H. in haemorrhage could be due to:

1. Greater parenchymal damage in haemorrhagic lesions.
2. Concomitant admixture of C.S.F. with blood, which further raises the cerebrospinal fluid L.D.H. enzymatic activity.

(c) Enzyme levels and prognosis

On comparison of mean peak C.S.F. enzyme levels between improved and expired cases of diagnostic groups, interesting findings emerged. Significantly higher cerebrospinal fluid G.O.T. and L.D.H. values were found in cases who expired in comparison to improved cases (P < 0.001 and < 0.01 respectively, Table-XIII). Regarding cerebrospinal fluid G.O.T. similar views have been expressed by Singh et al (1972), Kaul et al (1976) and Kohli et al. (1976). Wolints et al. (1969), Badi et al (1974) and Chaudhri et al. (1976) have observed similar increments in cerebrospinal fluid L.D.H. and related them to worsening of prognosis.

Higher values were found in deteriorating patients and expired cases. This may be chiefly due to the greater extent of cellular damage produced in such cases, Mandali et al. (1969) also have reported that significant elevation...
for C.S.F. enzymatic activity occurred only with patients suffering from large infarcts.

When serum G.O.T. levels were compared it was found that significant differences existed between improved and expired cases in case of haemorrhagic lesions only ($P < 0.001$). It may be that in haemorrhagic lesions the higher serum G.O.T. activity (as compared to infarction) raises the sensitivity of this estimation.

(d) **Diagnostic significance of Enzyme Levels:**

Maximum C.S.F. enzyme levels (G.O.T. and L.D.H.) were found in cases of haemorrhagic lesions. Similar have been the findings of Singh et al (1972), Bedi et al (1974), Chaudhari et al (1976), Kohli et al (1978, 81) and Kaul et al. (1978). However, the above findings are at variance with the observation of Laha and Shargava (1964) who did not report any variation in enzyme levels between various cerebrovascular accidents. No critical diagnostic levels could be obtained in this work, Kaul et al (1978) reported similar findings. Significantly higher values of serum G.O.T. were obtained in cerebral embolism as compared to thrombosis ($P < 0.05$). Due to small number of cases, it is difficult to deduce any conclusion from this. C.S.F. enzyme levels (G.O.T. and L.D.H.) were however, insignificant on comparison.

Highly significant differences in cerebrospinal fluid G.O.T. and serum G.O.T. ($P < 0.001$) were obtained on comparing subarachnoid haemorrhage to cerebral haemorrhage.
No significant differences in cerebrospinal fluid L.D.H. could be found (P ≥ 0.01).

Higher values in cerebral haemorrhage may be in part due to greater parenchymal damage present in such cases along with the contribution of contamination by blood.

C.S.F. AND SERUM ENZYME LEVELS IN MENINGITIDES:

(a) Tuberculous meningitis:

All cases showed a significant elevation of cerebrospinal fluid G.O.T. and L.D.H. from the time of admission (P < 0.001). Peak levels were obtained on admission itself and showed an decline thereafter, but were statistically significant during second week also. Rise in cerebrospinal fluid G.O.T. has been reported also by Green et al. (1957)*.

* Aronson (1961), Srivastava et al. (1971), Radly et al. (1972), and Khanna et al. (1977). Our findings are at variance with those of Shirolo and Nair (1974) and Praharaj (1979) who reported normal C.S.F. G.O.T. levels in cases of tuberculous meningitis. In the present study serum G.O.T. and L.D.H. were found to be normal in both varieties of meningitis. This may be because of lack of cellular damage in these cases. Out of 8 cases the improved. 3 showed sequelae in the form of lateral rectus palsy, optic atrophy and right sided hemiparesis. However, enzyme levels of cerebrospinal fluid G.O.T. and L.D.H. in these 3 were statistically insignificant as
compared to enzyme levels in rest of the improved cases (P > 0.05). No critical prognostic levels could be ascertained.

On comparing mean peak cerebrospinal fluid G.O.T. and L.D.H. levels between improved and expired cases significant difference was found in cerebrospinal fluid G.O.T. levels (P < 0.05). Cerebrospinal fluid L.D.H. levels did not show any significant difference (P > 0.05). Therefore in the present study cerebrospinal fluid L.D.H. levels did not vary with the ultimate clinical outcome of the cases of tuberculous meningitis, whereas higher cerebrospinal fluid G.O.T. levels were associated with a bad prognosis. Cerebrospinal fluid G.O.T. levels were not found to be of distinct diagnostic significance in a proper clinical setting. However cerebrospinal fluid L.D.H. levels were quite higher (91.0±41.3 I.U./L). This finding is in agreement with the observation of Kharma et al. (1977) who said that cerebrospinal fluid L.D.H. levels could be of help in diagnosing controversial cases of tuberculous meningitis with inconclusive C.S.F. findings. C.S.F. enzyme values showed a falling tendency on the subsequent follow up. This could serve as a guide to success of therapy. Similar were the findings of Wroblewski et al. (1958) and Feldman et al. (1973).

No correlation between C.S.F. enzyme levels of G.O.T. and L.D.H. with cell count or protein levels could be found. Similar findings have been reported by Kharma
et al. (1977) and Hallock et al. (1978).

(b) Pyogenic meningitis:

Cerebrospinal fluid G.O.T. and L.D.H. levels were significantly raised \( (P < 0.001) \) in all the ten cases of this illness, from the time of admission. Highest enzyme values were obtained on admission and a significant level above the normal was present on first followup.

The above findings are in consonance with those of Wroblewski (1957, 58), Aronson (1960), Lending et al. (1964), Beatty et al. (1968), Neches and Platt (1969), Reddy et al. (1972), Shirole and Nair (1976), Feldman et al. (1975), Hallock et al. (1978), Praharaj et al. (1978) and Gupta et al. (1982). No changes in serum G.O.T. and L.D.H. levels could be detected.

Extremely high mean peak C.S.F. enzyme levels were obtained in this group.

On comparing mean peak cerebrospinal fluid G.O.T. and L.D.H. levels between improved and expired cases significant variations in enzyme levels were found \( (P < 0.05 \) and \( < 0.001 \) respectively). However on comparing individual cases, out of 10 patients there were four expired cases. Fifty percent of them had cerebrospinal fluid G.O.T. values between 15 – 20 I.U./L, and rest had values above 20 I.U./L. Two out of four expired cases had cerebrospinal fluid L.D.H. values between 150 – 200 I.U./L and rest had values more than 200 I.U./L.
Higher values of cerebrospinal fluid G.O.T. and L.D.H. are therefore related to a bad prognosis. Similar findings have been reported by Reddy et al. (1972), Beatty et al. (1968), Belsey (1969) and Gupta et al. (1982). Shirde and Nair (1974) however could not correlate cerebrospinal fluid G.O.T. levels with course and prognosis of the disease.

The enzyme levels fall with therapy to lower values on subsequent follow-up. Cerebrospinal fluid L.D.H. levels serving as an index to success of therapy in pyogenic meningitis have also been reported by Wrblewski et al. (1958) and Feldman et al. (1975).

Extremely high cerebrospinal fluid L.D.H. values were obtained in all cases of pyogenic meningitis. Similar findings have been reported by Beatty et al. (1968), Hallock et al. (1978) has suggested that evaluation of cerebrospinal fluid L.D.H. may help in the diagnosis of culture negative pyogenic meningitis.

No correlation between cerebrospinal fluid G.O.T. and L.D.H. values and cell count and protein content of C.S.F. could be achieved. A relationship between cerebrospinal fluid G.O.T. levels and protein content of C.S.F. has been observed by Miyasaki et al. (1955), Srivastava et al. (1971) and Reddy et al. (1972). Shirde and Nair (1974) observed an association of cerebrospinal fluid G.O.T. levels with cellular content of C.S.F. A semiquantitative relation of leucocyte count with cerebro
spinal fluid L.D.H. in pyogenic meningitis was reported by Wroblewski (1958). However no such relationship was reported by Katzman et al. (1957), Beaty et al. (1968) and Neshes and Platt (1968). Findings in the present study are similar to those of latter group of workers.

THE BIOCHEMICAL GROUP:

(a) Transient ischaemic attacks:

Out of three patients of transient ischaemic attacks, none showed any variation of serum or C.S.F. enzyme levels. These findings are in conformity with those of Lieberman et al. (1957) who contended that mild or transient episodes of cerebrovascular insufficiency did not cause elevations of C.O.T. activity in serum. Similar observations in C.S.F. or serum have been reported by Mathur et al. (1963), Davies Jones (1970) and Singh et al. (1972). The normal levels of both enzymes in C.S.F./serum could be due to absence of frank cellular damage in these cases.

(b) Cortical vein thrombosis:

Statistically significant elevations of G.O.T. and L.D.H. were observed in the two cases studied under this group. No change was observed in serum levels. Higher serum and C.S.F. G.O.T. levels have also been reported by Singh et al. (1972), Kohli et al. (1978) reported raised cerebrospinal fluid G.O.T. levels in their three cases. However Kaul et al. (1978) reported that C.S.F. G.O.T. levels in their three cases were within normal limits. The
lack of studies on a sizeable number of patients under this group prevents one from further comments on these patients.

c) *Encephalitis:*

Encephalitis was diagnosed in three patients. None of them had any significant alteration in serum/C.S.F./G.O.T./L.D.H. levels. Similar findings have been reported by Myerson et al. (1957), Lending et al. (1964) and Gupta et al. (1982).

Beatty et al. (1969) found slight elevations in cerebrospinal fluid L.D.H. in viral infections of the nervous system. The normal levels of enzymes could be of value in differentiating this group from other types of meningitides where C.S.F. reports are inconclusive (e.g. partially treated meningitis of any etiology).