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Glutamic oxalacetic transaminase, lactic dehydrogenase, and creatine phosphokinase content in cerebrospinal fluid

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THE presence of the enzymes glutamic oxalacetic transaminase (GOT), lactic dehydrogenase (LDH), and creatine phosphokinase (CPK) in human cerebrospinal fluid (CSF) has been investigated by several authors,[1-11] in order to determine the changes that occur in various clinical conditions. Conflicting and often contradictory results have been reported,[12] particularly in regard to chronic neurologic diseases.

It has been postulated that destruction of tissues rich in GOT, LDH, and CPK initiates the release of these enzymes. An increase in the amount of any of these enzymes in fluids bathing the tissues would therefore indicate damage of such tissues. As applied to the central nervous system (CNS) the assumption has been made that a disorder severe enough to cause structural damage would result in the liberation of detectable amounts of GOT, LDH,‡[13] and CPK[14] into the CSF. Since it has been demonstrated that these enzymes do not freely cross the blood-brain and blood-CSF barriers,[16] the likelihood exists that abnormal amounts detected within the confines of the barrier would signify damage to the CNS.

Most investigators have agreed that there is significant increase in the enzyme content of the CSF in patients with acute disorders of the CNS such as cerebrovascular accident,[17] trauma,[18] and meningoencephalitis.[19-23] However, there are divergent opinions in regard to the enzyme values in subacute and chronic, progressive diseases with a long natural history and, at times, an almost imperceptible onset. These are the diseases for which there are no reliable laboratory tests that confirm the diagnosis in an early phase or identify a recrudescence of the disease. Therefore, it would be useful to develop an objective test that would establish the presence or absence of disease, and indicate active or quiescent phases of disease. The purpose of this study was to find out whether changes in the levels of these enzymes could help in this regard.

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‡ *There is evidence that 1 g of gray matter contains 80,000 U of LDH.*[15]

Materials and methods

Three hundred and seventy-one patients comprised this study (*Table 1*). In 37 a diagnosis of neurologic disease was excluded. The remaining 334 patients had various acute or chronic neurologic disorders. No attempt was made to select patients according to the severity or stage of the disease. The GOT, LDH, and CPK values were determined in specimens of CSF of all the patients, and the serum content was measured in most patients. The CSF was obtained by lumbar puncture; the first specimen of 3 ml was used to determine the cell count, protein content, globulin flocculation, and V.D.R.L. test; the second specimen of 3 ml to determine enzyme values. If pneumoencephalography was performed three specimens were obtained. Protein electrophoresis and other studies were done when indicated. All CSF specimens were centrifuged to avoid contamination by erythrocytes, and were analyzed within 24 hours of collection. Specimens containing more than 1000 erythrocytes per cubic millimeter were excluded from the study.

The GOT, LDH, and CPK values were determined using Technicon methodology on a single-channel analyzer. The values in 25 control subjects were determined in order to establish the normal range. Most of the control subjects were patients hospitalized to undergo elective surgical procedures, and the spinal fluid specimens were obtained at the time of spinal anesthesia. Patients with neurologic disorders or with diseases known to increase the serum GOT, LDH, or CPK values were not included as control subjects. The ages of the 25 control subjects were in the range of 15 to 85 years.

The statistical upper limit of normal values for each enzyme in CSF was calculated by adding 2.5 standard deviations to the mean value. The results, in units per milliliter are as follows:

	Mean value	SD	Statistical upper limit of normal value	Upper limit adopted
GOT	15.3	4.4	26.3	26
LDH	39	10.7	65.3	65
CPK	1.6	1.6	5.6	5.5

In our laboratory the normal range of serum GOT values is 20 to 40 Wacher units per milliliter; LDH values, 200 to 700 Wroblewski units per milliliter; and CPK values 0 to 13.5 Sigma units per milliliter.[24]

Results

Eighty-six patients (24 percent) of the 371 studied showed increased values of one or more enzymes in the CSF.

Glutamic oxalacetic transaminase. The patients whose CSF values were above normal for the enzyme GOT, and their diagnoses are listed in *Table 1.* A total of 41 patients (11 percent) had abnormal values. Two patients had no known

Table 1.—Data of 371 patients

Diagnosis	Elevations in cerebrospinal fluid, patients, number			Patients studied, total
	GOT	LDH	CPK	
* Demyelinating disorder (multiple sclerosis and similar diseases)	1	3	10	85
† Cerebrovascular accident	6	12	3	37
‡ Seizure disorder	0	1	2	30
Dementia (progressive presenile and senile)	5	5	0	21
Encephalopathies (metabolic, toxic, febrile, unknown)	4	7	2	18
Parkinson's disease	2	3	0	18
Peripheral neuropathy	3	2	0	17
Amyotrophic lateral sclerosis	2	2	1	9
Central nervous system metastasis	3	5	1	8
Radiculopathies	1	2	1	7
Cerebellar degeneration	1	0	0	7
Vertigo (peripheral)	0	0	0	6
Transient ischemic attacks	0	1	0	5
Spastic paraparesis	0	0	0	5
Guillain-Barré syndrome	2	1	0	5
Collagen-vascular disorders	1	0	0	5
Hypertensive encephalopathy	0	1	0	5
Myelopathies (cervical spondylosis)	0	2	0	4
Cryptococcal meningitis (one had intrathecal Amphotericin B)	2	4	0	4
Atypical facial pains and headaches	1	0	0	4
Viral meningoencephalitis	0	0	0	3
Heterogeneous system degeneration	0	0	0	3
Neurosyphilis	1	0	0	3
Infantile chronic encephalopathies (unknown etiology)	1	1	0	3
Spino-cerebellar degeneration	0	1	0	3
Cord tumor	0	0	0	2
Brain tumor	0	1	0	2
Radiation myelopathy	0	0	0	2
Huntington's chorea	2	1	0	2
Alcoholic encephalopathy	0	0	0	2
Psychosis (unclassified)	0	0	0	1
Creutzfeldt-Jakob disease	1	1	0	1
Brachial plexus neuritis	0	0	0	1
Pyomyelia	0	1	0	1
Pseudotumor cerebri	0	0	0	1
Bell's palsy	0	0	0	1
Hemifacial spasm	0	0	0	1
Extrapyramidal disease (unclassified)	0	0	0	1
Myeloma and peripheral neuropathy	0	0	1	1
No neurologic diagnosis	2	0	0	37
Total	41	57	21	371

* Acute and chronic.

† All cases studied within one month of the original insult.

‡ None post-ictal.

neurologic disease, demonstrated no GOT elevation in serum and had otherwise normal CSF. The highest value, 142 units per milliliter (serum content 100 units per milliliter) was demonstrated in the CSF of a patient with anoxic encephalopathy; the second highest value, 92 units per milliliter (serum content 67 units per milliliter) in the CSF of a patient with Creutzfeldt-Jakob disease. Nine patients had elevations of GOT in serum. Associated LDH elevations in CSF were found in 22 specimens, and associated CPK elevations in two. Associated protein elevations in CSF occurred in 19 patients and associated increase in leukocyte count in eight. GOT elevation in CSF was the sole abnormality in 14 specimens. The nosologic group most frequently associated with increased amounts of this enzyme in CSF was cerebrovascular accident (six patients—16 percent of all patients with cerebrovascular accident studied), followed by dementia (five patients—23 percent of all patients with dementia studied).

Lactic dehydrogenase. Fifty-seven (17 percent) patients had LDH values above normal in CSF (*Table 1*). The highest value of LDH was 700 units per milliliter (serum content, 2600 units per milliliter) and occurred in the CSF of a patient with anoxic encephalopathy; the second highest value was 430 units per milliliter (serum content 640 units per milliliter) in the CSF of a patient with diabetic hyperosmolar coma. Eight patients demonstrated elevations of the serum LDH. Associated CPK elevations occurred in four CSF specimens. Associated protein elevations in CSF occurred in 22 patients and associated increase in leukocyte count in 12. LDH elevations were the sole abnormality found in 44 CSF specimens. Twelve patients (33 percent) of the 37 patients with cerebrovascular accident had LDH elevations in CSF, and this was the disease most frequently associated with increased values. All patients with abnormal values of LDH in the CSF had neurologic disease.

Creatine phosphokinase. A total of 21 patients (7 percent of all the patients studied) demonstrated abnormal values of CPK in CSF (*Table 1*). The highest value was 11 units per milliliter (serum content 9.5 units per milliliter) in the CSF of a patient with multiple sclerosis. Five patients had elevations of the serum values. Associated protein elevations in CSF occurred in five patients and associated leukocyte elevations in three. In nine patients the CPK elevation was the only abnormality found in the CSF. Ten patients (12 percent of the 85 studied with demyelinating disorders) had CPK elevations in CSF. In this group of ten patients there were eight patients with optic neuritis and/or atrophy of the optic nerves; seven patients were in a period of exacerbation, and four patients revealed associated increase of the γ-globulin fraction in the CSF as measured by electrophoresis.

Discussion

It has been reported[25, 26] that the values of the enzymes GOT, LDH, and CPK in the CSF are independent of those in serum, and our results confirm this observation. In a few instances we found a concomitant elevation of the enzymes in serum and CSF; whether these elevations are coincidental or a

function of each other is not known. Therefore, until the behavior and functions of the blood-brain and blood-CSF barriers are better understood, it is advisable to obtain enzyme values in both serum and CSF and at the same time be particularly careful in interpreting high CSF levels associated with increased serum enzyme content.

In two instances, a GOT elevation above normal in CSF was found with no clinical evidence of neurologic disease. It is not known whether this apparent anomaly represented a false-positive value,[27, 28] an expression of unrecognized neurologic disease, or a laboratory error. The LDH and CPK elevations in CSF always have been in association with a neurologic disease.

Twenty-four percent of all the patients studied, representing a wide variety of neurologic entities, showed abnormal values of one or more enzymes in the CSF. Only 19 percent of the total number of patients had increased amounts of protein in the CSF. Approximately 5 percent of specimens showed concomitant enzyme and protein abnormalities. Therefore, the simultaneous determinations of enzyme and protein content demonstrated some alteration of the CSF in approximately 40 percent of the patients. This suggests that the determination of enzymes in the CSF will enable one to detect an additional 20 percent of patients who have structural disease of the CNS.

A widespread error committed in the past which has discredited the CSF enzyme values as a clinical test has been the attempt to use these enzyme determinations in the diagnosis of specific diseases. Obviously diverse etiologic factors can cause the ultimate pathologic consequence of tissue damage or destruction and hence release of the enzymes into the CSF. Thus, if the enzyme determination is to be used for diagnostic purposes, its utility will be as an indicator of structural damage to the CNS, independent of etiologic or pathogenetic factors. The experience derived from the present study confirms the observation that a great variety of acute, subacute and chronic neurologic disorders cause elevation of the enzyme values in the CSF, and that the only factor those diseases have in common is the ability to inflict structural damage to the CNS.

At most, it is possible to hypothesize over some differences found between diseases that affect primarily the gray matter and those that damage the white matter. The CSF of patients with cerebrovascular accidents, encephalopathies, and diseases that principally affect the gray matter, such as presenile and senile dementias, Creutzfeldt-Jakob disease, and Huntington's chorea has tended toward most often increased values of GOT and LDH. In contrast, the CSF of patients with demyelinating disorders has shown elevated CPK values. In a previous study[29] it was found that demyelinating diseases may cause a small but significant increase of CPK content in CSF, and it was proposed that demyelination be added to the list of causes of increased CPK values in CSF. The present report lends support to those earlier findings.

It is important to point out that patients with some diseases usually described as showing no abnormalities of the CSF may present abnormal values of one or more enzymes in the CSF. This occurred in patients with Parkinson's dis-

ease, Creutzfeldt-Jakob disease, Huntington's chorea, and peripheral neuropathy. The abnormalities found in the first three entities can be explained on the basis of cell destruction. The cause of the abnormalities found in the CSF of some patients with peripheral neuropathy is not clear, but may be an extension of the pathologic process to the nerve roots that are immediately in contact with CSF.

Finally, with reference to the problems presented in the introduction concerning the relapsing or progressive, chronic, degenerative diseases, it can be concluded that an elevation of the enzyme values in CSF confirms within reasonable limits the presence of a disease capable of inflicting structural damage to the CNS. Such increases may aid in the early distinction between functional and organic diseases of the CNS. In multiple sclerosis the elevation of CPK in CSF suggests an active disease process.

Summary

The normal values of the content of the enzymes glutamic oxalacetic transaminase, lactic dehydrogenase, and creatine phosphokinase in cerebrospinal fluid were established in 25 control subjects. Specimens of cerebrospinal fluid from 371 patients were analyzed; 24 percent of the patients had increased values, probably indicative of structural damage to the central nervous system. Increased amounts of GOT and LDH in CSF occurred most often in patients with acute, extensive diseases of the CNS and in patients with chronic diseases that preferentially damage the gray matter. Increased amounts of CPK in the CSF occurred predominantly in patients with demyelinating disorders.

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