Spinal fluid and blood serum enzyme activity in brain injuries

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Four enzymes have been investigated in spinal fluid and blood serum in two series of humans with varying degrees of brain injury. The values have been compared to those in a series of animals with standard experimental brain lesions. The enzymes studied showed high values, usually corresponding to the clinical severity of the injury, but not all figures are statistically significant. The highest values were found between the second and the ninth day following injury. The ultimate possibility of practical quantitative evaluation of brain injuries is discussed.

KEY WORDS · brain injury · enzyme · blood serum · cerebrospinal fluid

The enzyme activity in the central nervous system is poorly understood compared to that in some other organs, such as the liver and heart. Enzyme activity has been investigated in inflammatory, vascular, and hereditary diseases and in tumors, while only little is known about the enzymatic processes in brain injuries.

The purpose of this study was to investigate any correlation between the activity of several brain enzymes and the severity of the injury, and to find a method that would allow quantitative evaluation of brain injuries. The study was also expected to provide an insight into the dynamics of the enzyme exchange mechanism and the relationship between serum and spinal fluid values.

Material and Methods
The study included human and animal series. The following enzymes were investigated in both series: glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), malate dehydrogenase (MDH), and fructose 1, 6-diphosphate aldolase (ALD). GOT and GPT were investigated in all cases, while MDH and ALD were investigated in the animal series, in all Group 1 patients with slight injuries, and in two of the severely injured patients in Group 2.

Clinical Studies
The clinical series was divided into two groups. Group 1 included 10 patients with slight brain injuries, those patients who were unconscious for less than 1 hour. Group 2 consisted of 21 patients with severe brain injuries, those patients who were admitted in coma or semicoma and remained in this state for a week or more. All injuries were caused by the so-called “acceleration-deceleration” mechanism. We excluded all patients over 40
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years old, those with signs of systemic disease (for instance, heart or liver), those with multiple injuries, and those who had blood in the cerebrospinal fluid (CSF). Because most patients have the latter finding, very few were eligible for this study.

Nine of the 21 patients in Group 2 (with severe injuries) died; of the 10 patients in Group 1 (with slight injuries), none died.

In Group 2, simultaneous blood and CSF specimens were initially taken daily, and later randomly as indicated by the clinical picture. Specimens often had to be discarded for such reasons as hemolyzed serum or artificial blood in the CSF. Group I samples were taken only on the first day after injury. In all, 510 studies were performed on 199 specimens.

Animal Studies

The animal series consisted of 14 cats. The purpose of this series was to trace enzyme activity in the 3 days following a standardized brain injury. In each, a burr hole was made in the right frontal skull region in an anesthetized cat. Then a metallic cylinder 8 mm in diameter was placed on the intact dura, filled with liquid nitrogen, and left there for 90 seconds. After hemostasis the wound was sutured.

Six animals died during the experiment. Sectioned brains of dead animals showed uniform, superficial, conical lesions, 8 to 10 mm in diameter and 12 to 15 mm in depth. The induced lesions were extensive in proportion to the volume of the cats' brains.

Serum and CSF samples were taken 1 hour prior to making the lesions and 1 and 3 days after. All specimens contaminated by blood were discarded; in all, 256 studies were performed on 64 specimens.

Results

Clinical Studies

The results of the studies on humans are summarized in Figs. 1-4, representing single enzyme values in serum (S) and CSF (L).

The statistical significance of the difference between values obtained from Group 1 patients and those from survivors in Group 2 were as follows:

- SGOT: p = 0.1 to 0.05 (possibly significant)
- SGPT: p = 0.05 to 0.02 (significant)
- LGOT: p = 0.01 (highly significant)
- LGPT: p = 0.1 to 0.05 (possibly significant).

The limited number of MDH and ALD studies in the group of severely injured patients does not allow a statistical evaluation. Therefore the average values presented
in Table 1 are for the two groups and should be considered simply as an orientation.

Animal Studies

The data are summarized for blood serum in Fig. 5 and for CSF values in Fig. 6. As in the human series, the MDH values are omitted because of inconsistent findings.

Discussion

Although reports dealing with enzyme changes in the central nervous system are rare, few body systems represent a more interesting model for investigations of this type. Of particular interest are the unique phenomena of the blood-brain barrier and the independent organ circulation represented by the CSF.

The enzymatic reaction, or more properly stated, the appearance of enzymes in body fluids, depends mainly on the speed of enzyme loss from a damaged cell and its dispersion in the extracellular spaces, where degradation of enzymes and the rate of transport from CSF to blood play important roles. The concentration of enzymes is considerably higher in the cell than in the extracellular space. This is valid for the enzymes investigated, but not for all others. Therefore, the working hypothesis was that enzyme values in the spinal fluid, which could be considered extracellular space, increase after trauma to the nervous system, or to nerve cells in blood serum following damage to the blood-brain barrier.

There are several mechanisms that cause damage or death to cells. In our cases hypoxic damage and destruction may have been the most important.
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The differences between enzymatic values in lethal and nonlethal cases are obvious in human serum, but less pronounced in spinal fluid. Quantitatively, the differences in the two groups are rather small, because the question of death and survival was not entirely the result of the degree of brain damage, but also was due to extracranial complications such as pulmonary or renal failure. Moreover, the number of specimens in the deceased group was considerably smaller. Some patients died in the first 2 days, before the enzyme levels reached their peak.

The most reliable and consistent results were obtained with GOT and to a lesser degree with GPT, while MDH values proved to be completely unreliable. The investigation of aldolase seems promising, but further studies performed on a larger scale will be needed to confirm this impression.

Our general impression is that the serum values, and to a lesser degree those in spinal fluid, are elevated in proportion to the severity of the brain damage. There is a correlation between serum and CSF values. The rising serum values for GOT and GPT in the deceased group contrast with the decreasing values among the survivors. The fact that CSF values do not follow this pattern suggests that extracerebral factors may be responsible.

The dynamics of enzyme release were similar in all the enzymes investigated. If we omit some unexplained elevations and depressions, the highest values are found in the period from the second to the ninth day after injury. This is true for both CSF and blood serum values. These elevated values continued for 20 days and longer.

Wolintz, et al., found that SGOT values in patients with brain infarctions reached their peak after 100 hours; Singh, et al., found LGOT peaked on the third and fourth days, and Lieberman, et al., found SGOT and LGOT reached their maximum levels on the second day. It was observed that the return to normal value seems to take longer in serum than in CSF.

No attempt was made to find a relationship between enzyme levels and the amount of protein in CSF, nor was the role of cellular elements studied. A number of patients have been treated by hypothermia. We do not consider this factor in this report, but Miwa, et al., found lower values in serum and uncertain changes in spinal fluid in GOT, GPT, and lactate dehydrogenase (LDH).

In the animal series the results are similar to those in the human series, at least during the time investigated. Aldolase and GOT behaved very consistently, and GPT somewhat less so; as in humans, we were not able to obtain a uniform MDH pattern in the animal series. Possibly this can be explained by the fact that a relatively small series makes the normal deviations more prominent.

At present it seems doubtful if the evaluation of brain damage after trauma is possible on a quantitative basis. One of the most important arguments would be the impossibility of distinguishing between damage to different anatomical regions. Obviously, there is a functional and prognostic difference between a lesion in the brain stem and one of comparable size in the frontal lobe. This becomes less important if we consider the fairly constant and similar pattern of anatomical

![Fig. 6. CSF values for GOT, GPT, and aldolase in the animal series. (U = unit, D = day.)](image_url)
changes after brain injuries caused by the acceleration-deceleration mechanism. Another source of dubious results may be our limited knowledge about enzyme dynamics. It has not been determined whether enzyme loss from a destroyed cell is greater than that from a damaged one. Further, circulatory disturbances may influence enzyme transport. Another possibility is that the enzyme content may vary in different neural structures. Miyazaki found considerable differences in transaminase concentrations in specific brain areas.

On the basis of present knowledge, we conclude that enzyme studies cannot be considered a reliable prognostic method in the evaluation of brain injuries. The practical clinical use of enzyme studies may remain limited to selected cases, such as chronic encephalopathies and patients in whom the clinical findings are inconsistent.

Most certainly, further investigations should be initiated to find specific cerebral isoenzymes. This knowledge would help eliminate the possible errors due to the release of enzymes from other tissues; it would also provide insight into the enzyme metabolism of the brain cell, and ultimately might lead to the development of a laboratory method for quantitative evaluation of brain trauma.

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References


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