Creatine phosphokinase in the cerebrospinal fluid

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In 1935, Lehmann described the enzyme creatine phosphokinase (CPK) which catalyses the reversible transfer of phosphate between adenosine diphosphate (ADP) and creatine phosphate (Lehmann 1935, 1936):

Creatine phosphokinase exists in greatest concentration in skeletal muscle tissue, followed by brain and heart (Colombo, Richterich, and Rossi, 1962). Recent work has demonstrated the presence of several isoenzymes of creatine phosphokinase in heart, skeletal muscle, and brain (Burger, Richterich, and Aebi, 1964; Sjövall and Voigt, 1964).

Dreyfus, Schapira, and Demos (1960) have recently pointed out the advantage of determining serum levels of this enzyme in the investigation of muscle disease. Colombo *et al.* (1962), Hughes (1963), and others (Ebashi, Toyokura, Momoi, and Sugita, 1959), have found high levels of creatine phosphokinase in the serum of patients with progressive muscular dystrophy. These levels may also be useful in the diagnosis of acute myocardial infarction, especially in differentiating between myocardial and pulmonary infarction (Dreyfus, Schapira, Resnais, and Scebet, 1960; Stich and Tsirimbis, 1962). Acheson, James, Hutchinson, and Westhead, (1965) found that 15 of 24 patients with cerebrovascular accidents (other than subarachnoid haemorrhage) had an elevated serum creatine phosphokinase level. This elevation did not correlate well with the site of the lesion nor of its extent but had some prognostic significance. Workers in the United States have failed to show a regular elevation of the serum creatine phosphokinase level after a stroke.

Creatine phosphokinase is thought to play an important role in cerebral metabolism by maintaining ATP concentrations under resting conditions and after activity, restoring these concentrations at the expense of creatine phosphate of the tissue (McIlwain, 1959). Herschkowitz and Cumings (1964)

have studied the creatine phosphokinase activity of the cerebrospinal fluid using the method of Tanzer and Gilvarg (1959). The results in this report represent further inquiry using another method for the estimation of creatine phosphokinase. This investigation was undertaken concomitantly with Herschkowitz and his colleagues in London and continued in Philadelphia.

METHOD

Cerebrospinal fluid specimens were obtained from patients at the National Hospital for Nervous Diseases, Queen Square, and the Hospital for Sick Children, Great Ormond Street, London, and the Hospital of the University of Pennsylvania and the Philadelphia General Hospital, Philadelphia. These patients were referred for evaluation of neurological symptoms. The majority of the fluids were obtained from the lumbar sac and the remainder from the lateral ventricles. The specimens were taken during the course of diagnostic investigation, and when the patient required air encephalography, the specimen for analysis was obtained before the injection of air. Ten spinal fluids obtained from the lumbar sac immediately before the induction of spinal anaesthesia were studied as a control group of 'normal' patients. These individuals were undergoing elective surgery for non-neurological diseases, *e.g.*, gallstones, hernia, varicose veins, etc. Protein concentration and cell counts were performed on most specimens. When possible, the creatine phosphokinase activity was estimated after collection but, when this was impracticable, specimens were stored at -25°C . for not longer than two months and then analysed.

Hughes' (1962) method for measuring serum creatine phosphokinase was modified for the estimation of the enzyme in the cerebrospinal fluid by doubling the amount of specimen used. The concentration of the other reagents was adjusted to maintain the required volume in the mixture to be analysed. The level of creatine phosphokinase in the specimen is expressed in international units/ litre and calculated according to Hughes (1962).

RESULTS

Of one hundred patients studied, 61 had cerebrospinal fluid creatine phosphokinase levels of 0 to 0.5

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Table I shows the distribution of 100 cases with the number of 'normal' versus the number of elevated levels of creative phosphokinase. The χ^2 test performed upon the data in this table gives a value of 36.9 with 14 degrees of freedom. The p value is less than 0.001, making unlikely the possibility that the distribution resulted from chance alone.

<i>Distribution of Cases</i>	<i>No. of Cases</i>	<i>No. 'Normal'</i>	<i>No. Raised</i>
Control patients	10	10	0
Tumour of central nervous system	20	8	12
Vascular lesions	12	8	4
Herniated intervertebral disc	7	6	1
Pseudo-tumour	1	1	0
Multiple sclerosis	5	5	0
Polyneuritis (including Guillain-Barré syndrome)	3	3	0
Cerebral atrophy	3	3	0
Meningitis (bacterial and viral)	2	1	1
Epilepsy	6	4	2
Optic atrophy	2	2	0
Hydrocephalus (stable)	3	2	1
Hydrocephalus (progressive)	1	0	1
Dementia	6	6	0
Miscellaneous	19	19	0
Totals	100	78	22

Consistently elevated enzyme levels were found in the spinal fluids of patients with chromophobe adenomas whilst those with meningioma all had normal enzyme levels. These results are comparable with those of Herschkowitz and Cumings (1964). The other tumours fell between these two extremes, so that, in all, 60% of tumours of the central nervous system studied had an elevated cerebrospinal fluid creatine phosphokinase. It is interesting that the spinal fluid creatine phosphokinase levels were repeatedly in the normal range in a patient who was referred for recurrent ocular symptoms some

The superscripts refer to the numbers in the miscellaneous column.

There is no correlation of the cerebrospinal fluid creatine phosphokinase activity with the cerebrospinal fluid protein, cell count, or serum creatine phosphokinase activity.

The cerebrospinal fluid creatine phosphokinase was determined in 12 patients with cerebrovascular disease. In this group of patients there were five who had transient cerebral ischaemia and, therefore, little, if any, destruction of brain tissue. None of these patients had elevated creatine phosphokinase levels in the cerebrospinal fluid. Of the remaining seven patients, five had accomplished strokes with attendant tissue necrosis and two of these had elevated enzyme levels. Another patient had recurrent episodes of ischaemia with some neurological residuum and his creatine phosphokinase was elevated. There was no correlation between the number of erythrocytes in the cerebrospinal fluid (one guide to the proximity of the lesion to the subarachnoid space) and the creatine phosphokinase levels. There does, however, seem to be a rough association between the actual amount of tissue infarcted and the level of creatine phosphokinase in the cerebrospinal fluid.

DISCUSSION

There is an easily measurable level of creatine phosphokinase in the cerebrospinal fluid of some patients with neurological disease. A group of control patients was studied and none had elevated enzyme levels. Of the 22 patients with elevated creatine phosphokinase levels, 12 had central nervous system tumours. No meningiomas were associated with an elevated level and the same was true in a case of spinal cord compression from an epidural metastasis of prostatic cancer. All the cases of chromophobe adenoma studied had elevations of the spinal fluid creatine phosphokinase whilst the same was true only for some of the patients with infiltrating gliomas. There was no relationship between the amount of tumour necrosis and the level of creatine phosphokinase in the spinal fluid.

It would seem that external compression of the brain or spinal cord (as in meningioma) is not sufficient to cause a release of the enzyme into the cerebrospinal fluid and that actual infiltration or infarction of normal tissue is necessary to raise the enzyme level. Herschkowitz (1964) has shown that the creatine phosphokinase level in tumour tissue is lower than that in surrounding normal brain and this may lend further credence to the aforementioned hypothesis.

It is of interest that none of the patients with cerebellar lesions had a creatine phosphokinase level above 2.2 i.u./l. Its concentration in cerebellar white matter is relatively low (Colombo *et al.*, 1962) so that tissue damage in this region might well lead to a smaller enzyme release into the cerebrospinal fluid than equivalent lesions in other parts of the brain.

The results of the study of cerebrovascular lesions are interesting in that none of the patients with transient cerebral ischaemia leaving no neurological residuum had an elevated spinal fluid creatine phosphokinase level whilst one patient with recurrent ischaemia and residuum did have an elevated level of the enzyme. Another of the patients in this group, who presumably had a small vascular lesion (Pari-*naud's syndrome*), also had a normal enzyme level. Further study is needed to clarify the relationship of the enzyme to cerebrovascular disease, especially during the evolution of an infarction. Hopefully, closer correlation of the enzyme changes with pathological findings can be obtained.

Herschkowitz (1964) has found that the creatine phosphokinase level in cerebrospinal fluid is helpful in determining the status of hydrocephalus, *i.e.*, stable versus progressive. In this series we found that the one case of progressive hydrocephalus was associated with an elevated enzyme level and one of

three cases of stable hydrocephalus also had an elevated level. More work on this aspect of creatine phosphokinase might provide a useful guide in helping the clinician to decide when cerebrospinal fluid shunting operations are necessary.

No cases of dementia or multiple sclerosis were associated with an elevated spinal fluid creatine phosphokinase and this finding may prove useful in the differential diagnosis of certain lesions.

The former study (Herschkowitz, 1964) further cites the usefulness of determinations of the enzyme in distinguishing symptomatic from idiopathic epilepsy. We studied six cases of idiopathic epilepsy and found normal enzyme levels in four. One specimen from a case with an elevated creatine phosphokinase level was obtained in the immediate postictal period and this may have some bearing on the results. If further work bears out the premise that one can often distinguish the two forms of epilepsy on the basis of the level of the enzyme in the cerebrospinal fluid, then the determination may help in the decision as to which patients should have cerebral angiography after their first seizure even with no localizing neurological findings.

SUMMARY

Cerebrospinal fluid specimens from 90 patients with neurological disorders and 10 from control patients were analysed for creatine phosphokinase levels. There was no elevation of the level of this enzyme in the spinal fluid of the control patients. Seventy-eight per cent of the patients studied had normal enzyme levels, less than 1.5 i.u./l. Of the 22 patients with elevated creatine phosphokinase in the cerebrospinal fluid, 12 had tumours of the central nervous system and four had cerebrovascular disease.

Twenty tumours of the central nervous system were studied and 60% of them had an elevated enzyme level. All the cases of chromophobe adenoma (4) had elevated levels whilst those of meningioma had consistently normal levels. Cases with other tumours fell in between.

A rough correlation exists between the level of the enzyme in the cerebrospinal fluid and the amount of tissue infarcted in cerebrovascular accidents. The enzyme level in the cerebrospinal fluid does not rise in transient cerebral ischaemia without residuum. An elevation of the level has not been seen in multiple sclerosis (five cases) or dementia (six cases).

The possible usefulness of creatine phosphokinase levels in cerebrospinal fluid in determining the status of hydrocephalus and in separating idiopathic from symptomatic epilepsy is discussed.

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