Cerebrospinal fluid creatine phosphokinase in acute subarachnoid hemorrhage

SAMUEL H. GREENBLATT, M.D.

Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire

The author measured the level of creatine phosphokinase (CPK) in 35 cerebrospinal fluid (CSF) specimens from 30 patients with acute subarachnoid hemorrhage, and correlations were sought with 17 other clinical and laboratory parameters. Elevations of CSF CPK have no diagnostic specificity. However, they do show a statistically significant correlation with the existence of any destructive process in cerebral tissue (hydrocephalus, infarction, intraparenchymal hemorrhage, or intraventricular clot). Yet arterial spasm without infarction does not raise the CSF CPK level. During the preoperative management of ruptured aneurysms and vascular malformations, a significant elevation of the CSF CPK level can thus provide a clue to the presence or significance of one or more of these destructive processes.

KEY WORDS • cerebral aneurysm • arteriovenous malformation • cerebrospinal fluid • creatine kinase • subarachnoid hemorrhage

In the initial management of acute subarachnoid hemorrhage (SAH), one of the greatest concerns is to know whether there is associated brain tissue damage, especially when aneurysm surgery is anticipated. The common usage of clinical grading systems is based on this premise. Hence, the potential existence of other parameters of the brain's pathophysiological status merits serious consideration. Since mammalian erythrocytes contain only negligible amounts of creatine phosphokinase (CPK), 5,18 Wolintz, et al.,19 found cerebrospinal fluid (CSF) CPK levels especially appropriate as indicators of parenchymal damage in SAH. However, all of their 17 SAH patients were very severely ill, and 14 died. They did not give final pathological data for their series, but it appears that most of their patients had massive intraparenchymal hemorrhages. With the exception of a few other random cases, 5,8 there are no reports on CSF CPK in SAH. The present study was undertaken to determine whether the measurement of CSF CPK levels would be useful in the differential diagnosis and management of acute SAH. Our results have shown that CSF CPK elevations have no diagnostic specificity, but they may be useful in management because they are indicative of parenchymal brain damage, even in the presence of bloody CSF.

Materials and Methods

Clinical Material

The series was comprised of 30 patients admitted to the Dartmouth-Hitchcock Affiliated Hospitals between May 1, 1971, and May 31, 1972. Twelve patients had aneurysms, and two had vascular malformations; parenchymal hemorrhages or hemorrhagic
infarcts were eventually proven in four. Four others suffered complications of various kinds of accidental or iatrogenic trauma, and the cause of the SAH was never determined in eight. There were 18 males and 12 females. The age range was 2 months to 86 years. The mortality rate in the entire group was 33%, including three patients who died after clipping of their aneurysms.

Method

Only those cases of SAH confirmed by atraumatic lumbar puncture (LP) or ventricular tap (in an infant) are included. No patient was ever tapped solely to obtain a CSF CPK. Concomitant serum CPK's were drawn within a few hours of the corresponding LP. Only 0.1 or 0.2 cc of serum or CSF respectively were required. Specimens were taken immediately to the clinical laboratory and centrifuged. If they could not be run immediately, they were frozen at −15° to −18°C and stored overnight or over the weekend. All serum and CSF samples were run as part of the routine laboratory work. The reagents are contained in the Calbiochem CPK Stat-Pack,* which used the “forward reaction” method of Rosalki.14 The results are expressed in International milliunits per milliliter (mU/ml). Normal serum levels in our laboratory are 5 to 40 mU/ml. “Normal” trace levels in CSF are not measurable by this technique.

The CSF CPK values were not revealed to the investigator or to any member of the clinical team until after the patient had been discharged from the hospital or had died. Serum values were posted in the clinical charts. At the end of the study the charts and radiographs were reviewed and the CPK values and correlated clinical data were analyzed with the aid of a Honeywell 635 computer. Among the various parameters with which correlations were sought, certain pathophysiological phenomena commonly associated with SAH proved to be the most interesting, namely, arterial vasospasm, hydrocephalus, ischemic infarction, and intraparenchymal and intraventricular hematomas.

Since vasospasm and hydrocephalus are not static lesions in the acute state, they were considered to be positively or negatively correlated with each individual CSF CPK determination only if an appropriate investigative study had been performed on the patient within 24 hours of the time when the CSF specimen was obtained. In other words, if a CSF CPK was obtained from a patient on a certain date, a correlation was sought with the presence or absence of vasospasm only if an arteriogram had been performed on that patient within 24 hours before or after the time when the LP was done. The same time strictures were also applied to diagnostic studies for hydrocephalus. Whenever possible, the diagnosis of significant hydrocephalus was made arteriographically, using the ventriculo-cranial index described by Bergvall and Galera.2 This index is the ratio of the width of one lateral ventricle to the width of the ipsilateral hemisphere as measured from the anteroposterior (AP) projection of the venous phase of a carotid arteriogram. Significant hydrocephalus is considered to be present only when the index ratio is 0.33 or more. Appropriately timed arteriograms with adequate AP views of the venous phase were available for correlation of this index with 14 CSF CPK's. In a few other instances significant hydrocephalus was considered to be present when it was grossly obvious in a ventriculogram or in a cisternogram.

Decisions about the time of onset of infarctions and hematomas had to be made on the basis of the clinical records for each patient, and correlations with these processes were then sought for all CSF CPK's obtained from that patient after the onset of the infarction or hematoma. The diagnosis of ischemic infarction was confirmed by technetium brain scan in all cases except two. In these two exceptions, the diagnosis was accepted on very strong clinical grounds after arteriographic study had shown no other possible explanation for the clinical picture. Surgical or autopsy confirmation was available for all cases of intraparenchymal and intraventricular hematomas. All appropriate clinical and laboratory criteria were used to make the best possible decision about the time of onset, and positive or negative correlations with CSF CPK's were decided accordingly.

*The Calbiochem CPK Stat-Pack is manufactured by Calbiochem, P.O. Box 12087, San Diego, California 92112.
Results

A total of 55 CSF CPK's were obtained from 30 patients, with 28 concomitant serum values. Six of the 55 CSF CPK's were taken postoperatively, which included the highest CSF CPK in the study (110 mU/ml). Although most of the other postoperative CSF CPK's were much lower, it was felt that all of these values were rendered uninterpretable by the inherent vagaries of direct surgical manipulations of the brain. Hence, the conclusions stated below are based on analyses of the remaining 49 preoperative CSF CPK's.

Summary of Test Results

The mean value of the 49 preoperative CSF CPK's was 4.2 mU/ml. The range was 0 to 49 mU/ml, including 13 CSF's with no detectable activity and seven with only 1 or 2 mU/ml. A similar paucity of CSF CPK was noted by Wolintz, et al.,\textsuperscript{10} in several of their SAH patients. These findings are consistent with the theoretical assumption that the simple presence of blood in the subarachnoid space should not cause a significant elevation of CPK in the CSF, except by dilution of the serum CPK that is spilled into the CSF during the hemorrhage. Even a massive SAH spills no more than a few cc's of blood into the CSF.\textsuperscript{19} If 5 cc of blood contain a total of 200 mU of CPK, then diluting this in 100 cc of CSF should result in a CSF CPK level of 2 mU/ml. Evidence below indicates that CSF CPK levels higher than 2 to 3 mU/ml are usually associated with destructive processes in the central nervous system (CNS).

Negative Results

No significant correlations were found between CSF CPK levels and: age, sex, time after SAH, serum CPK, CSF pressure, CSF protein, CSF erythrocyte count, systemic blood pressure, cerebrovascular spasm, and final etiologic diagnosis. The range of the 26 preoperative serum CPK's was 10 to 220 mU/ml, with a mean of 78 mU/ml. The absence of a correlation with CSF levels had been anticipated on the basis of several previous reports.\textsuperscript{5,8,10,11,17,19} Serum CPK's can be raised even by intramuscular injections,\textsuperscript{4} which would certainly be a hazard for any group of sick patients in an intensive care unit.

TABLE 1

<table>
<thead>
<tr>
<th>CSF CPK (mU/ml)</th>
<th>Number of Associated CSF CPK's</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Destructive Processes</td>
</tr>
<tr>
<td>0 - 1.5</td>
<td>0</td>
</tr>
<tr>
<td>2 - 3.5</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>11</td>
</tr>
</tbody>
</table>

Significant Correlations

Truly significant results were obtained in correlations of elevated CSF CPK levels with evidence of destructive processes in the CNS, that is, hydrocephalus, infarction, parenchymal hematoma or ventricular clot. There is no diagnostic correlation with any particular type of process, but a high CSF CPK is a fairly reliable indicator of its presence. This can be expressed in two analyses that are clinically useful:

Association with a Destructive Process. Among 27 CSF CPK's in the range from 0 to 3.5 mU/ml, only four (15%) were definitely associated with a destructive process. On the other hand, among the 22 CSF CPK's higher than 3.5 mU/ml, 11 (50%) were known to have such an association. This difference is statistically significant (p < 0.01 by the chi-squared test). In Table 1 these data are displayed in three CSF CPK ranges in order to show that none of the CPK's in the range from 0 to 1.5 mU/ml were associated with a destructive process. Since it is obviously impossible to have complete information about all of these destructive processes for each patient, it is quite likely that the 50% association of the CSF CPK's over 3.5 mU/ml is artificially low.

Association with Cerebrovascular Spasm. Cerebrovascular spasm was not considered to be of significant proportions unless it was clearly associated with an arteriographic disturbance of flow in at least one major intracranial branch of the carotid or vertebral-basilar circulation. Even then it was not counted as a destructive process per se, though any associated infarction was. Among the three patients who had only significant spasm (without infarction), the mean CSF CPK was 1.7 mU/ml. But the mean CSF
CSF creatine phosphokinase in acute SAH

CPK for 15 specimens known to be associated with destructive processes (with or without spasm) was 8.0 mU/ml. This difference is also statistically significant (p = 0.02 for a one-sided alternative in a t-test assuming unequal variances).

A major disappointment in the composition of this series was the absence of any hemorrhagic tumors. It has been shown in other studies that non-hemorrhagic tumors frequently cause an abnormally high CSF CPK. \(^8,10,11,13,17\) In our series there are two contrasting cases which lend credence to the claim that the presence of a pre-existing mass lesion will be signalled by a high CSF CPK. Cases 12 and 15 both had acute massive cerebral hemorrhages with essentially similar clinical pictures. Case 12 had no symptoms prior to the day of ictus except probable hypertension, and no other etiology was discovered at autopsy. His CSF CPK was 3.5 mU/ml. Case 15, on the other hand, had a 5-year history of intermittent vertigo and a 1-year history of severe headache. A non-neoplastic vascular malformation was found at surgery. His CSF CPK was 41 mU/ml.

Statistically Unproven Trends

There were discernible trends toward positive correlations between elevations of CSF CPK and 1) poor clinical grade,\(^8\) 2) increasing ventricular size (ventriculocranial index)\(^8\) without overt hydrocephalus, and 3) poor status on follow-up. However, the wide ranges of the CPK values and their standard deviations precluded the achievement of statistical significance for these parameters. Another potentially important but quite unproven trend concerned surgical prognosis. Three of the four patients who had poor results after direct aneurysm clipping had had CSF CPK's greater than 3.5 mU/ml within the two weeks prior to surgery, but none of the three surgical patients with good results had shown such high CSF CPK levels.

Discussion

Most previous studies of CSF CPK activity have either assumed or concluded that the presence of elevated CPK levels in the CSF is indicative of parenchymal damage.\(^7,12,16,19\) The present study was designed partly as a test of this hypothesis, and it has been confirmed. Within the context of acute SAH, the conclusions to be drawn from the foregoing results are: 1) the presence of blood in the CSF does not raise the CSF CPK level significantly, except by spillage of serum CPK into the CSF during hemorrhage; 2) the actual CSF CPK value has no diagnostic specificity; 3) tissue-destructive processes in the CNS will engender abnormal levels of CSF CPK; 4) cerebrovascular spasm without infarction does not cause an elevation of CSF CPK. In addition, it would appear likely that the level of elevation of CSF CPK is roughly proportional to the extent of parenchymal brain damage, but the data derived from the present study are not statistically sufficient to substantiate such a claim.

With regard to the initial management of acute SAH, the above conclusions may be helpful in two ways. First, a CSF CPK level higher than what might be expected from serum spillage should make one suspicious that some destructive process is present. If it cannot be immediately identified, further diagnostic studies may be required. Second, if a patient has both spasm and an elevated CSF CPK, the spasm cannot be called to account for the CPK elevation. For example, if arteriography in a deteriorating patient reveals both spasm and hydrocephalus, a low CSF CPK would indicate that the patient's poor condition is attributable to the spasm alone, but a high CSF CPK would speak for a functionally significant element of hydrocephalus.

Despite the optimistic tone of the preceding remarks, it is obvious that, from the biochemical standpoint, the basic method of this investigation was rather crude. In fact, there are two isoenzymes of CPK, one of muscular and one of cerebral origin.\(^1,6\) The next step in the pursuit of refinement for this study will be to measure these isoenzymes separately in the CSF, since the isolation of CSF CPK elevations derived solely from cerebral tissue would be a better indicator of brain damage.

Acknowledgments

This work was supported in part by a grant from the Hitchcock Foundation (Fund 250E). Dr. Elizabeth French and Elizabeth Jenkins, supervised the CPK determinations and Carol Simpson performed the statistical analyses. Drs. French, Ernest Sachs, Jr., Richard Saunders, and Kenneth Shulman gave valuable guidance and reviewed the manuscript.
References


This paper was presented in part to the New England Neurosurgical Society, Dedham, Massachusetts, June 1, 1973.

Address reprint requests to: Samuel H. Greenblatt, M.D., Department of Neurological Surgery, Albert Einstein College of Medicine, Bronx, New York 10461.