Creatine kinase isoenzymes in acute brain injury

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Brain-type creatine kinase (CK) isoenzyme (CK-BB) was detected in the serum in 13 out of 26 patients with acute brain injury (50%). The peak of CK-BB activity ranged from 5 to 188 U/liter, constituting, on average, 10.5% of the total CK activity. The highest activities were seen in patients with gunshot wounds. High CK-BB activity was associated with poor prognosis, but minimal CK-BB elevations did not have prognostic significance.

Heart-type creatine kinase isoenzyme (CK-MB) was detected in the serum in 17 out of 26 patients (65%). The peak activity ranged from 5 to 115 U/liter, constituting, on average, 6.6% of total CK activity. Electrocardiograms taken from 20 patients revealed transient T-wave inversions in the precordial leads in four patients; three of them also showed serum CK-MB activity. Subendocardial hemorrhage was detected at autopsy in three of the five CK-MB-positive patients, but in none of the four CK-MB-negative cases. Present findings suggest that acute brain injury may secondarily cause myocardial damage.

KEY WORDS • head injury • alcohol intoxication • cerebral concussion • acute brain injury • creatine kinase isoenzyme • electrocardiography • myocardial infarction

Biochemical diagnosis of acute brain damage has traditionally been confined to analysis of cerebrospinal fluid. No specific blood test has been available, and there has been uncertainty whether such a test could be devised because of the blood-brain barrier. We have previously shown that CK-BB, the creatine kinase isoenzyme typical of brain tissue, is released from brain to blood after experimental and clinical brain injury. The findings have been confirmed by others using similar electrophoretic techniques, by chromatographic methods, and recently by radioimmunoassays.

There is substantial evidence to suggest the occurrence of myocardial damage in various types of cerebrovascular disorders. In a previous study, we frequently found CK-MB, the isoenzyme associated with the heart, in the serum of patients with cerebrovascular disorders, thus supporting the evidence obtained earlier experimentally and by electrocardiographic (EKG) changes. It is not known whether similar myocardial lesions occur also in patients with traumatic brain injury.

The present study was carried out to ascertain the frequency of CK-BB and CK-MB elevations in traumatic brain injury, and to see if the possible isoenzyme elevations could be correlated to the severity of brain damage or to ultimate prognosis.

Clinical Material and Methods

The clinical material consisted of 26 patients with acute brain injury. Twenty-one of them were male and five female. The mean age of the patients was 29 years, with an age range from 5 to 69 years.

The severity of brain injury was graded according to the time of unconsciousness ("unconsciousness" was defined as the inability to obey commands or to utter recognizable words. Eye opening was not included, in contrast to the Glasgow Coma Scale). Ten patients had a mild brain injury, and had been unconscious less than 30 minutes; four patients had a
FIG. 1. Peak values of brain-type creatine kinase isoenzyme (CK-BB) in 26 patients with acute brain injury. Black circle = died; half circle = survived. Lined area indicates cases in which no CK-BB activity was detected.

moderate brain injury, and had been unconscious between 30 minutes and 6 hours; and 12 patients had a severe brain injury, and had been unconscious for 6 hours or more. Twenty-four patients had a closed head injury; two of them had an epidural hematoma and two others had an acute subdural hematoma. Two patients had a gunshot wound of the head. Six of the 26 patients had severe extracranial injuries: two patients, both of whom died, had a chest injury with rib fractures, and four others had at least one fracture of the long bones. The overall mortality was 38%; nine of the 10 deaths occurred within the 1st hospital week, and autopsy was carried out in all nine. Outcome of the survivors was assessed at 6 months according to the Glasgow Outcome Scale.

Blood samples were collected on admission and daily during the first 3 days. The first sample was obtained within 6 hours of the injury in 22 cases and at latest within 22 hours. Serum samples were stored at \(-20^\circ\text{C}\) for at most 2 months before the analysis. Total CK activity was measured spectrophotometrically at \(37^\circ\text{C}\), and demonstrated an upper limit of 220 U/liter for men and 170 U/liter for women. The isoenzymes were separated electrophoretically on cellulose acetate and quantified fluorometrically. Normal serum does not show any CK-BB or CK-MB activity with this method. The method detects an isoenzyme band corresponding to a CK activity of 3 U/liter as measured in the spectrophotometer at \(37^\circ\text{C}\). A standard 12-lead EKG was recorded on admission and during the first 3 hospital days. Blood alcohol concentration was measured only from the first blood sample by gas chromatography.

TABLE 1

<table>
<thead>
<tr>
<th>Time After Trauma (hrs)</th>
<th>CK-BB</th>
<th>CK-MB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Value (U/liter)</td>
</tr>
<tr>
<td>2.4 ± 0.4</td>
<td>11</td>
<td>46.5 ± 16.1</td>
</tr>
<tr>
<td>10.0 ± 1.0</td>
<td>5</td>
<td>15.0 ± 3.0</td>
</tr>
<tr>
<td>34.2 ± 5.5</td>
<td>2</td>
<td>7.0</td>
</tr>
</tbody>
</table>

* Results expressed as mean ± standard error of the mean.
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TABLE 2

<table>
<thead>
<tr>
<th>Severity of Brain Injury</th>
<th>No. of Cases</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Good Recovery</td>
</tr>
<tr>
<td>mild</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>moderate</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>severe</td>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>

* Causes of death: pulmonary abscess and diabetic ketosis.

Results

The brain-type CK isoenzyme (CK-BB) was detected in the serum in 13 out of the 26 patients (50%). The peak CK-BB activity ranged from 5 to 188 U/liter (Fig. 1), amounting on average to 10.5% of the total CK activity (range 0.9% to 24.4%). The two highest activities were seen in patients with gunshot wounds, both of whom died. Maximum CK-BB activity was usually detected in the first sample taken on admission (Table 1). Only one patient with moderate brain injury showed no CK-BB activity in the first sample taken 5 hours after the injury, but the second sample taken 11 hours later showed a CK-BB activity of 21 U/liter. The occurrence of CK-BB activity was transient in all cases (Fig. 2).

If the patients with severe and moderate brain injuries are taken together and compared with those with only a mild brain injury, it can be seen that in both groups half of the patients revealed serum CK-BB activity (Fig. 1). Three of the four patients with CK-BB activity higher than 50 U/liter died, whereas only one of the nine CK-BB-positive patients with CK-BB activity lower than 50 U/liter died, and in this case death was caused by pulmonary abscess. The absence of CK-BB activity in serum was not necessarily a good prognostic sign because six CK-BB-negative patients also died. Five of the six patients with multiple injuries showed serum CK-BB activity.

The age of the patients did not correlate with the occurrence of serum CK-BB activity; nor was there any correlation between CK-BB activity and blood alcohol concentration, although half of the patients were found to be intoxicated on admission. On the other hand, the severity of brain injury correlated well with the outcome of the patients (Table 2).

Heart-type CK isoenzyme (CK-MB) was detected in 17 out of the 26 patients (65%). Its peak activity ranged from 5 to 115 U/liter (Fig. 3), constituting, on average, 6.6% of total CK activity (range 1.9% to 14.0%). Highest values were usually found in the first sample (Table 1), but the decay was not, however, as rapid as with CK-BB. No CK-MB activity was found later than 54 hours after the head injury. Five of the six patients with multiple injuries showed serum CK-MB activity. Highest CK-MB activities were measured in patients with severe brain injury, although CK-MB activity was detected most often in patients with mild injury (Fig. 3). Serum CK-MB activity was revealed more often in younger than in older patients: it was detected in 11 of the 14 patients under the age of 30 years, while it was detected in six of the 12 patients older than 30 years of age. There was no correlation between the blood alcohol concentration and serum CK-MB activity.

Routine 12-lead EKG's from 20 patients revealed transient inversion of T-waves in the precordial leads in four patients, three of whom showed CK-MB activity. Six patients with severe or moderate brain injury did not have EKG recording; all of these had CK-MB activity.

Autopsy was carried out in nine cases. Subendocardial hemorrhage was detected in three of the five CK-MB-positive cases, but in none of the four CK-MB-negative cases. The outcome of the patients did not
correlate with EKG changes suggestive of myocardial lesion.

Discussion

Thirteen (50%) of our 26 patients showed CK-BB activity in the serum within a few hours of head injury, and the three patients showing highest CK-BB activity died. The results support the claim proposed earlier that CK-BB is readily released from brain to blood after widespread diffuse brain damage. On the other hand, six of the 10 patients who died showed no CK-BB activity in the serum a few hours after brain injury.

One explanation of the results is that in some cases the brain injury can be critical although the actual area of brain tissue damaged is not very large. Furthermore, some of the CK-BB-negative patients died from extracerebral causes such as pulmonary abscess or diabetic ketosis. If the tissue destruction is extensive, CK-BB attains higher values and the outlook tends to become grave. The results therefore suggest that the finding of CK-BB in the serum does not itself mean a bad prognosis, but high CK-BB levels

Although the brain injury may have been confined to a small area only, there was obviously destruction of brain tissue in all the cases. The reason for half the cases remaining CK-BB-negative is not known. It can be due to enzyme inactivation or due to the insensitivity of our method of measurement. Creatine kinase CK-BB isoenzyme has been shown to be labile in the serum in vivo, but the rapid inactivation in vitro may have been critical in some cases. Further studies are needed to clarify this possibility, especially since a new technique has recently been introduced to prevent the inactivation in vitro. Several techniques other than electrophoresis exist for measuring CK isoenzymes, although they may be less convenient for routine clinical use. Rabow and Hedman, using a chromatographic technique, found CK-BB activity in 12 patients with cerebral laceration or contusion. Radioimmunoassays are more sensitive, and preliminary results showed increased levels of CK-BB in patients with traumatic lesions. Further studies are needed, however, to exclude the possible cross-reactivity of CK-MB isoenzyme in radioimmunoassays.

Methodological improvements may therefore be expected to increase the percentage of CK-BB-positive findings in acute brain injury. It is not possible at the moment to predict if serum CK-BB isoenzyme determinations will become sensitive enough to reveal clinically silent brain tissue damage as enzyme tests do in diseases of heart, liver, and muscle. The present methods, however, seem to give some kind of an estimate of severe brain damage, even when single samples are analyzed. More information could possibly also be obtained by analyzing serial samples, similarly to the way serial CK-MB determinations are used for quantifying myocardial damage.

The presence of CK-MB isoenzyme in the serum was introduced in 1973 as a specific test for myocardial damage, and our subsequent experiences confirm the usefulness of this test. This isoenzyme can be detected in the serum in muscle diseases also, especially in muscular dystrophies, but traumatic muscle lesions very seldom cause the appearance of CK-MB in the serum. The finding of CK-MB isoenzyme in the serum in 17 of 26 patients (65%) therefore suggests that acute brain injury is often accompanied by acute concomitant myocardial damage. Further evidence is obtained from autopsy results and EKG changes.

The results are in accordance with our earlier studies on patients with subarachnoid hemorrhage and with other cerebrovascular disorders. The mechanism of myocardial damage in these conditions is unsettled. It has been suggested that elevated plasma catecholamines might cause myocardial damage in cerebrovascular disorders. Increased catecholamines have recently been observed in the plasma of patients with acute head injury, which suggests a similar humoral mechanism of myocardial damage in both conditions. Myocardial contusion due to chest trauma could explain some of the findings, but it cannot be the main cause, since chest trauma was seen in only two of the 26 patients. The curious conversion of CK-BB to a band electrophoretically indistinguishable from CK-MB, that has been observed in vitro, could be offered as the sole explanation, unless there were no other findings suggestive of myocardial involvement. Electrocardiographic and autopsy findings, however, exclude this possibility.

Myocardial involvement in traumatic brain injury presents as subendocardial lesions at autopsy. Patients with cerebrovascular disorders show similar lesions, and in those cases the myocardial involvement, as suggested by EKG changes and CK-MB elevations, is associated with poor prognosis. The same trend was not observed in patients with traumatic brain injury, but the series was rather small, and the patients were usually much younger than those suffering from cerebrovascular disorders. It is therefore possible that myocardial involvement may be critical in some cases with traumatic brain injury. It is important to recognize this complication, especially because it can be prevented by medical treatment.
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References


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