Measurement of Serum Alkaline Phosphatase Isozyme I in Brain-damaged Patients

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Abstract
The authors measured alkaline phosphatase isozyme I (ALP-I) in sera of 24 brain-damaged patients and four with disorders other than brain damage. The study population comprised three patients with postresuscitation encephalopathy, four with ruptured cerebral aneurysms, 14 with acute subdural hematoma and cerebral contusion, and three with nontraumatic intracerebral hemorrhage. ALP-I detected in brain damage is physicochemically different from the other known ALP-Is that appear in patients with obstructive jaundice or hepatoma. In the brain-damaged patients, ALP-I became elevated about 7 days after admission and markedly increased as secondary brain damage developed. Excluding patients who died within 9 days of admission, the maximum serum ALP-I concentration was well correlated with the functional outcome. In cases in which barbiturate therapy was effective, the appearance of ALP-I was delayed and its elevation was suppressed. The results of this study suggest that measurement of serum ALP-I is useful not only in the management but also in predicting the prognosis of brain damage.

Key words: alkaline phosphatase, brain damage, barbiturate

Introduction
In patients with head trauma or cerebrovascular disease, the severity of brain damage ultimately determines the outcome. Various techniques are commonly applied to assess the extent of brain damage, including neurological examination, brain imaging technologies, and electrophysiological monitoring. Recently, biochemical monitoring has attracted attention as a potential means to assess brain damage. In this investigation, we measured alkaline phosphatase (ALP) isozyme I (ALP-I), which we previously detected in brain-damaged patients, and studied the relationship between their measured levels and the outcome.

Patients and Methods
Twenty-eight patients admitted to the Department of Emergency Medicine, University of Tokyo from January through June, 1988 were included in the study. Three patients had postresuscitation encephalopathy (PRE), four had ruptured cerebral aneurysms (RCA), 14 had an acute subdural hematoma and cerebral contusion (ASDH), and three had nontraumatic intracerebral hemorrhage (NICH). Among the four patients who served as controls, one suffered a facial injury and one a brain concussion, and two were epileptics. Male to female ratio was 17 to 11 and the age ranged from 15 to 78 years old (mean, 42 years old). No patients had clinical evidence of hepatoma or obstructive jaundice.

Serum ALP-I was measured by the Bessy-Lowry method (normal range, 66–220 IU/l) and its isozyme pattern was determined by electrophoresis. In two RCA and one ASDH patients, ALP-I was also measured in cerebrospinal fluid (CSF). The three PRE patients were treated conservatively, without barbiturate therapy. In the NICH group, one patient underwent ventricular drainage with barbiturate therapy, one had hematoma removed, and the other received conservative treatment. Three of the four RCA patients underwent clipping of the aneurysm, one with postoperative barbiturate therapy. The remaining one RCA patient underwent ven-
tricular drainage with barbiturate therapy. The four patients with ASDH were treated conservatively. The remaining 10 patients with ASDH underwent removal of the hematoma, and six received postoperative barbiturate therapy. Thus, nine patients received barbiturate therapy, and its effectiveness was estimated from the point of controlling intracranial pressure (ICP).

Outcome was assessed 6 months after admission by the Glasgow Outcome Scale and was rated as good recovery, moderate disability, severe disability, persistent vegetative state, or death. The last group was subdivided into patients who died within 9 days of admission and those who survived beyond 9 days.

**Results**

The outcome of the 24 brain-damaged patients are given in Table 1. Five ASDH patients showed good recovery. One NICH patient exhibited moderate disability and one RCA patient severe disability. Among the four who were persistently vegetative were one with ASDH, two with NICH, and one with RCA. Six patients — two with PRE and four with ASDH — died within 9 days of admission. Seven died after the 9th day, including one with PRE, four with ASDH, and two with RCA. Barbiturate therapy was effective in four of the nine patients; whose outcomes were persistent vegetative state in two (one with RCA and one with NICH) and death after the 9th day in two (ASDH).

ALP-I was not detected in any of the four controls (Fig. 1). Among patients with brain damage, ALP-I was not detected in two of the five patients who showed good recovery. In the remaining three, it appeared only transiently at low levels. The moderately disabled patient had a maximum ALP-I concentration of 11 IU/l. On discharge, the patient who was severely disabled had a concentration of 69 IU/l. Among patients in a persistent vegetative state, maximum ALP-I values ranged from 40 to 160 IU/l. ALP-I was not detected in four of the six patients who died within 9 days of admission, and measured less than 16 IU/l in the other two. Among the seven patients who died after the 9th day of hospitalization, ALP-I increased to over 190 IU/l in five in whom barbiturate therapy was not administered or was ineffective. The maximum values in the two cases in which barbiturate therapy was effective were 24 and 184 IU/l. The concentration of ALP-I in the CSF of the three cases was under measurable range.

ALP-I concentration increased to over 100 IU/l in six patients in whom barbiturate therapy was not administered or was ineffective. In those patients, ALP-I generally appeared about 7 days after admission and increased markedly as secondary brain damage progressed (Fig. 2 upper). In four patients in whom barbiturate therapy was effective, the appearance of ALP-I was delayed and its serum concentration remained low (Fig. 2 lower).

In the 10 patients who were autopsied, the absence of hepatoma and obstructive jaundice was confirmed histologically.

**Discussion**

Several types of ALP isozyme have been identified in normal human serum, including hepatic (ALP-II), bone (ALP-III), placental (ALP-IV), and intestinal

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**Table 1** Outcome by cause of brain damage

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of cases</th>
<th>PRE</th>
<th>RCA</th>
<th>ASDH</th>
<th>NICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>GR</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MD</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PVS</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>D1</td>
<td>6 (2)</td>
<td>2</td>
<td>0</td>
<td>4 (2)</td>
<td>0</td>
</tr>
<tr>
<td>D2</td>
<td>7 (4)</td>
<td>1</td>
<td>2 (1)</td>
<td>4 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

The number in parenthesis represents cases in which barbiturate therapy was attempted. GR: good recovery, MD: moderate disability, SD: severe disability, PVS: persistent vegetative state, D1: death within 9 days of admission, D2: death after 10 days.
ALP-I in Brain Damage

ALP-I types. These isozymes differ enzymatically and immunologically. ALP-I is known to appear in cases of cancer\(^1\) and obstructive jaundice.\(^1\) We found that an ALP-I also appears in brain-damaged patients,\(^3\) and that this ALP-I has a molecular weight of about 150,000 and no tolerance to heat. The motility in the electrophoresis is lowered by Triton X100 and neuraminidase, and its activity is not inhibited by phenylalanine.\(^7\) On the other hand, the ALP-I that appears in obstructive jaundice is of high molecular weight, and that which appears in hepatoma is inhibited by phenylalanine. Therefore, the ALP-I detected in brain damage is physicochemically different from the other known ALP-I.s. In addition, in this study there was no evidence of obstructive jaundice or hepatoma.

Shimizu\(^9\) demonstrated ALP histochemically in vascular endothelium, choroid plexus, and the outer surface of the arachnoid membrane in several animals. He noted that there was more ALP in gray than in white matter and that it was especially prominent in the brainstem and in structures adjacent to the ventricular system. Shinonaga et al.\(^9\) reported that ALP activity decreased markedly in the walls of capillaries in experimentally induced cerebral swelling. It has also been suggested that\(^5\) ALP is involved in the transport of substances across capillary walls and glial cell membranes, that is, in the function of the blood-brain barrier. Thus, this type of ALP-I appears to recede from the damaged brain.

Figure 3 shows the ALP-I values in a case in which brain death resulted from cerebral swelling secondary to subarachnoid hemorrhage. Initially, the ALP-I value was low; however, after angiographical diagnosis of brain death, it increased markedly, finally reaching 1000 IU/l. In this case, barbiturate therapy failed to control the ICP (Fig. 4). Although the total ALP value also increased, the elevation of ALP-I was greater.

As illustrated in Fig. 1, in patients who died early, ALP-I was low or failed to appear. The reason for this is unclear. Generally, ALP-I was detected about 7 days after admission, concomitant with the progression of secondary brain damage (Fig. 2). It is possible that, among the early fatalities, cerebral blood flow ceased before ALP-I drained into the cerebral vessels from the damaged brain tissues. With the exception of this group, the outcome was well correlated with the ALP-I levels.

It is interesting that the appearance of ALP-I was delayed and its concentration remained low in patients in whom barbiturate therapy was effective in

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**Fig. 2** upper: Changes in serum ALP-I in six patients in whom the ALP-I concentration increased to over 100 IU/l (barbiturate therapy was not administered or was ineffective). lower: Changes in serum ALP-I in four patients in whom barbiturate therapy was effective. Case 1: PRE patient (outcome was D2); 2 and 3: RCA (D2); 4, 5, 8, and 9: ASDH (D2); 6 and 10: NICH (PVS); 7: RCA (PVS). Abbreviations are the same as in Table 1.

**Fig. 3** Serum ALP-I levels in an RCA patient who died on the 17th day of hospitalization (Case 3 in Fig. 2). The ALP-I concentration increased markedly after the clinical diagnosis of brain death. In this case, barbiturate therapy failed to control the ICP.
controlling the ICP (Fig. 2). Soulairac and Desclaux\(^{10}\) reported that ALP activity in the brain was suppressed in barbiturate-induced experimental coma. In addition to a direct effect of lowering ALP in the brain, barbiturates may suppress the elevation of ALP by preventing secondary brain damage.

References


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