Aldosterone, Catecholamines, and CK-BB 
as Biochemical Markers in Hypertensive 
 Intracerebral Hemorrhage

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Abstract

The author measured blood concentrations of aldosterone, epinephrine, norepinephrine, and creatine kinase isozyme (brain type)(CK-BB) in 65 patients with hypertensive intracerebral hemorrhage. The purpose of this study was to evaluate these measurements in determining the severity of acute cerebral damage in such patients. There were 42 males and 23 females ranging in age from 30 to 93 years. Their clinical status was classified as mild or severe on the basis of neurological grading. In the mild group, plasma aldosterone increased slightly at the onset of disease, while the other markers showed no change. In contrast, the severe group showed elevation of all markers on admission, with a gradual return to normal by day 3 to day 7 of hospitalization. Analysis of the data by hematoma site revealed that aldosterone levels increased in patients with thalamic hemorrhage; epinephrine and norepinephrine concentrations were high in those with pontine hemorrhage; and CK-BB levels were elevated in cases of thalamic and cerebellar hemorrhage. It was also noted that patients in whom all four markers were increased tended to have poor outcomes.

Key words: hypertensive intracerebral hemorrhage, aldosterone, catecholamine, creatine kinase

Introduction

Computed tomography (CT) has improved the accuracy of diagnosis of cerebrovascular disease, and its usefulness in this regard is undisputed. However, CT data alone do not provide sufficient information concerning the extent of brain damage and the effect of increased intracranial pressure.

Biochemical approaches to evaluate brain damage have been attempted by many investigators. Among the substances studied are pituitary hormone, catecholamines, and aldolase. The author measured blood levels of aldosterone, epinephrine, norepinephrine, and creatine kinase isozyme (brain type) (CK-BB), which are known to change in the acute phase of brain damage, and studied the relationships between these markers and the severity of brain damage.

Patients and Methods

The patients were 65 adults with hypertensive intracerebral hemorrhage (ICH) diagnosed by CT performed within 6 hours from the onset. They include 30 with putaminal hemorrhage, 16 with thalamic hemorrhage, six with pontine hemorrhage, five with cerebellar hemorrhage, and eight with subcortical hemorrhage (Table 1). The patients’ ages ranged from 30 to 93 years (mean, 61.6 years).

Blood samples were collected at the time of admission and on days 3 and 7 of hospitalization (a total of three times in the acute phase of the disease). Plasma aldosterone was measured by radioimmunoassay, serum epinephrine and norepinephrine by high performance liquid chromatography, and serum CK-BB by electrophoresis. Normal values were considered to be 47-131 pg/ml for aldosterone, 0.12 ng/ml or less for epinephrine, 0.05-0.40 ng/ml for norepinephrine, and 0-1 IU/l for CK-BB.

Status on admission was graded according to a previously described neurological classification. Patients were...
tients of grades 1 and 2 were assigned to the mild hemorrhage group and those with grades of 3-5 to the severe hemorrhage group.

The outcome was evaluated in accordance with the Glasgow Outcome Scale. Good recovery and moderate disability were classified as a good outcome, and severe disability, persistent vegetative state, and death as a poor outcome.

The results are given as means + SD. Differences in mean values were analyzed by Student’s t test.

Results

I. Mild hemorrhage (grades 1 and 2)

As shown in Table 1, there were 29 patients with mild hemorrhage. Figure 1 illustrates the findings in this group. On admission, mean plasma aldosterone levels were slightly elevated. They decreased significantly by day 3 and returned to normal by day 7. Serum epinephrine levels fluctuated within the normal range throughout the observation period. Serum norepinephrine also changed very little. Serum CK-BB levels showed minor changes within the normal range.

II. Severe hemorrhage (grades 3-5)

In the 36 patients in this group, the changes in the four biochemical markers were more pronounced (Fig. 2). The mean plasma aldosterone level was high at the time of admission, decreased significantly (p < 0.01) by day 3, and returned to normal by day 7. The serum epinephrine concentration was elevated at the time of admission, decreased markedly by day 3 (p < 0.01), and further decreased by day 7. The serum norepinephrine level was high at the time of admission, decreased significantly by day 3 (p < 0.01), and declined further by day 7. An increase in the mean CK-BB concentration was observed at the time of admission and on day 3. It returned to normal by day 7 (p < 0.05).

III. Relationships between the biochemical markers at the time of admission and the hematoma site

As Table 2 shows, there were clear correlations...
between the biochemical markers at the time of admission and the site of the hematoma. Aldosterone levels were higher in patients with thalamic hemorrhage than in those with hemorrhage at other sites. Epinephrine and norepinephrine levels were increased in the presence of pontine hemorrhage. CK-BB levels were elevated in patients with thalamic and cerebellar hemorrhage. In general, the concentrations of these markers tended to be low in patients with subcortical hemorrhage and high in those with pontine hemorrhage.

**Table 2** Changes in biochemical markers by site of hematoma

<table>
<thead>
<tr>
<th>Location of hematoma</th>
<th>Aldosterone (pg/ml)</th>
<th>Epinephrine (ng/ml)</th>
<th>Norepinephrine (ng/ml)</th>
<th>CK-BB (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td>176.8 ± 94.2</td>
<td>0.18 ± 0.33</td>
<td>0.50 ± 0.42</td>
<td>1.34 ± 1.14</td>
</tr>
<tr>
<td>(n=28)</td>
<td>(n=29)</td>
<td>(n=29)</td>
<td>(n=22)</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>216.5 ± 122.2</td>
<td>0.16 ± 0.21</td>
<td>0.35 ± 0.15</td>
<td>2.00 ± 3.05</td>
</tr>
<tr>
<td>(n=15)</td>
<td>(n=15)</td>
<td>(n=15)</td>
<td>(n=9)</td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td>192.3 ± 58.3</td>
<td>0.57 ± 0.53</td>
<td>0.90 ± 0.73</td>
<td>1.95 ± 1.27</td>
</tr>
<tr>
<td>(n=6)</td>
<td>(n=6)</td>
<td>(n=6)</td>
<td>(n=5)</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>188.0 ± 38.9</td>
<td>0.38 ± 0.34</td>
<td>0.57 ± 0.20</td>
<td>2.93 ± 2.42</td>
</tr>
<tr>
<td>(n=5)</td>
<td>(n=5)</td>
<td>(n=5)</td>
<td>(n=3)</td>
<td></td>
</tr>
<tr>
<td>Subcortex</td>
<td>148.8 ± 72.3</td>
<td>0.04 ± 0.05</td>
<td>0.42 ± 0.22</td>
<td>0.92 ± 0.63</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(n=8)</td>
<td>(n=8)</td>
<td>(n=7)</td>
<td></td>
</tr>
</tbody>
</table>

IV. The relationships between the biochemical markers at the time of admission and outcome (Fig. 3)

Lower aldosterone levels were associated with a better outcome, and this difference was significant (p < 0.05). Patients with lower epinephrine levels also had better outcomes, although this correlation was not significant. In the poor outcome group, norepinephrine levels were significantly higher than those in the good outcome group (p < 0.01). Finally, the CK-BB concentration was most strongly
correlated with outcome; patients with poor outcomes had a much higher mean CK-BB level than those with good outcomes (p < 0.01).

**Discussion**

In patients with cerebrovascular disease, precise knowledge of the severity of brain damage and the intensity of stress is very important in planning appropriate treatments. With cranial CT scanning, it is possible to identify the site of bleeding in patients with hypertensive ICH. However, although CT provides a great deal of anatomical information, it yields little information concerning cerebral metabolism.

In this study, the author evaluated four biochemical markers as indices of the severity of brain damage and the intensity of stress in patients with acute hypertensive ICH. In the acute phase, ICH is frequently associated with autonomic nerve dysfunction, including changes in blood pressure, excessive perspiration, and abnormalities of temperature and pulse rate. Catecholamines are considered useful parameters in the investigation of sympathetic nervous system activity. Serum norepinephrine is principally derived from the terminal of the sympathetic nervous system, and changes in its blood levels may sensitively reflect the activity of the sympathetic nervous system. Epinephrine is abundant in the medulla of the adrenal gland, but is scant in the brain and heart. Epinephrine in blood is derived mainly from the medulla of the adrenal gland. In acute cerebrovascular disease, which is associated with functional activation of the sympathetic nervous system and the medulla of the adrenal gland, serum catecholamine levels are probably elevated.

In this study, peak catecholamine levels were observed at the onset of illness. Kanda et al. reported peak levels within 2–3 days of onset, and Komatsu et al. observed peak levels approximately 3
days and 12 days after onset. The catecholamine concentration might be expected to peak on the day of onset, since the increase in blood pressure at this time suggests accelerated sympathetic nervous activity.

The plasma aldosterone level increases under anesthesia and at the time of surgery,4,9 and its usefulness as an indicator of stress is well known. The author found plasma aldosterone levels to be high in patients with severe head trauma and acute cerebrovascular disease.10,12 The increase in aldosterone was greater in patients with subarachnoid hemorrhage than in those with ICH or cerebral infarction.12 In patients with subdural hematoma, plasma aldosterone levels were correlated with the degree of midline shift as shown by CT.11 These observations suggest an association between the plasma aldosterone concentration and intracranial pressure.11

In the present study, too, aldosterone was elevated in severe cases and its concentration was well correlated with the outcome. Thus, plasma aldosterone appears to be a valuable stress index.

Comparison of the four parameters by site of hemorrhage revealed that, generally, aldosterone increased in thalamic hemorrhage, epinephrine and norepinephrine in pontine hemorrhage, and CK-BB levels in cerebellar and thalamic hemorrhage. Of course, determination of definite site specificity of these parameters requires considerably more research. However, the behavior the parameters studied indicates that they are influenced by separate mechanisms. The results reported here support the contention that blood levels of aldosterone, epinephrine, norepinephrine, and CK-BB are valuable in assessing the severity of brain damage and the intensity of stress.

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References


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