Early change of plasma and cerebrospinal fluid arginine vasopressin in traumatic subarachnoid hemorrhage

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Objective: To investigate the changes and effects of arginine vasopressin (AVP) in patients with acute traumatic subarachnoid hemorrhage (tSAH).

Methods: The plasma and cerebrospinal fluid (CSF) level of AVP, and intracranial pressure (ICP) were measured in a total of 21 patients within 24 hours after tSAH. The neurological status of the patients was evaluated by Glasgow Coma Scale (GCS). Correlation between AVP and ICP, GCS was analyzed respectively. Meanwhile, 18 healthy volunteers were recruited as control group.

Results: Compared with control group, the levels (pg/ml) of AVP in plasma and CSF (X±s) in tSAH group were significantly increased within 24 hours (38.72±24.71 vs 4.54±1.38 and 34.61±21.43 vs 4.13±1.26, P<0.01), and was remarkably higher in GCS ≤ 8 group than GCS > 8 group (50.96±36.81 vs 25.26±12.87 and 44.68±31.72 vs 23.53±10.94, P<0.05). The CSF AVP level was correlated with ICP (r=0.46, P<0.05), but no statistically significant correlation was found between plasma AVP, CSF AVP and initial GCS (r=-0.29, P>0.05 and r=-0.32, P>0.05, respectively). The ICP (mm Hg) in tSAH patients was elevated and higher in GCS ≤ 8 group than in GCS > 8 group (25.9±9.7 vs 17.6±5.2, P<0.05).

Conclusion: Our research suggests that AVP is correlated with the severity of tSAH, and may be involved in the pathophysiological process of brain damage in the early stage after tSAH. It seems that compared with the plasma AVP concentration, CSF AVP is more related to the severity of tSAH.

Key words: Arginine vasopressin; Subarachnoid hemorrhage, traumatic; Glasgow coma scale; Intracranial pressure
METHODS

All the procedures in this study were in accordance with the Ethics Committee of Zhejiang University. Patients from January 2004 to June 2006 were screened according to specific inclusion and exclusion criteria.

Clinical data
A total of 21 patients with acute tSAH (7 females and 14 males, aged from 19 to 62 years with a mean age of 34.63 years) were enrolled according to the following criteria: (1) hospitalization within 24 hours after brain injuries; (2) evidence of meningeal irritation (neck stiffness) and SAH approved by spinal tap and CT; (3) without concomitant serious injuries; (4) no severe underlying diseases prior to injuries; and (5) without any dysfunction of heart, lung, kidney or other important organs. The enrolled patients included 9 cases of cerebral contusion, 4 epidural hematoma, 3 subdural hematoma, 2 intracerebral haematoma and 3 without extra injury in the brain parenchyma by CT scanning. All patients in tSAH group were scanned with cranial CT and performed the spinal tap to authenticate the clinical diagnosis. Spinal tap was performed 8 hours (the time of one CSF circulation) after the brain injuries. Glasgow Coma Scale (GCS) scores were assessed when the patients were admitted. There were 10 patients with GCS>8 (the moderate injury group) and 11 patients with GCS ≤ 8 (the severe injury group). The 18 volunteers (6 females and 12 males, aged from 22 to 58 years, with a mean age of 35.47 years) in the control group had no abnormal findings on a clinical or laboratory base.

Sample collection and testing methods
Venous blood samples (2 ml) were collected in the morning at rest from the healthy volunteers and from the tSAH patients within 24 hours after traumatic brain injury (TBI). CSF (2 ml) was collected within 8 to 24 hours with spinal tap after TBI, meanwhile, ICP was tested. All the samples were put in pre-cooled centrifuge tubes containing 50 µl of 0.3 mol/L ethylene diamine tetraacetic acid sodium (EDTA-Na) and 5×10^5 U of trasylol, then centrifuged at 4°C, 3000 r/min for 10 minutes. All samples were stored at -70°C until being assayed. The levels of AVP were determined by radioimmunoassay (RIA) after extraction and concentration using SEP-PAK cartridges. The AVP level was measured in Hangzhou Radioimmunologic Center. Radioimmunoassay reagent kits were supplied by DSL Company, USA. The detecting instrument, γ-counting meter, was made by DPC Company, USA. All the samples were marked and measured with double blind method. All tSAH patients were treated with traditional therapy, including reducing the elevated intracranial pressure, administrating drugs, maintaining water and electrolytes homeostasis, and operation if necessary.

Statistical analysis
All the data were expressed as x ± s. Differences between groups were analyzed using the two-tailed Student’s t-test. Correlations between variables were assessed by the Spearman test. P<0.05 was considered statistically significant. All the offline analysis was performed by SPSS 13.0 software package (SPSS, Chicago, USA).

RESULTS

Correlation between plasma AVP and CSF AVP in patients with acute tSAH
Within 24 hours after tSAH, the mean AVP levels in plasma and CSF in tSAH group were significantly higher than those in control group (P<0.01). There was no significant difference between the plasma AVP and CSF AVP (P>0.01, Table 1). A positive correlation was found between the plasma and CSF AVP (r=0.661, P<0.05).

Relationship between plasma AVP, CSF AVP and GCS
There were 11 patients with severe brain injury (initial GCS ≤ 8) and 10 patients with mild or moderate brain injury (initial GCS>8). The mean AVP levels in plasma and CSF in GCS ≤ 8 group were significantly higher than those in GCS>8 group (P<0.05, Table 2). However, No statistically significant correlation was found between plasma AVP, CSF AVP and the initial GCS (r=-0.29, P>0.05 and r=-0.32, P>0.05, respectively, Table 3).

Relationship between plasma AVP, CSF AVP and ICP
The mean ICP in all patients with tSAH was (21.9 ±8.5) mm Hg, including 17 patients with intracranial hypertension (more than 20 mm Hg). ICP was significantly higher in GCS ≤ 8 group than in GCS>8 group (P<0.05, Table 2). Correlation between CSF AVP and ICP was statistically significant (r=0.46, P<0.05), while no obvious correlation was found between plasma AVP and ICP (r=0.34, P>0.05, Table 3).
Table 1. Comparison between plasma AVP and CSF AVP concentration in tSAH group and control group (pg/ml)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Plasma AVP</th>
<th>CSF AVP</th>
</tr>
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<tbody>
<tr>
<td>tSAH</td>
<td>21</td>
<td>38.72±24.71</td>
<td>34.61±21.43</td>
</tr>
<tr>
<td>Control</td>
<td>18</td>
<td>4.54±1.38</td>
<td>4.13±1.26</td>
</tr>
<tr>
<td>t value</td>
<td></td>
<td>6.327</td>
<td>6.505</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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</tbody>
</table>

Table 2. Comparison between plasma AVP, CSF AVP concentration (pg/ml) and ICP (mm Hg) in tSAH groups with different GCS

<table>
<thead>
<tr>
<th>Variables</th>
<th>GCS</th>
<th>ICP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma AVP</td>
<td>-0.29</td>
<td>0.34</td>
</tr>
<tr>
<td>CSF AVP</td>
<td>-0.32</td>
<td>0.46</td>
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</table>

Table 3. Correlation between plasma AVP, CSF AVP and GCS, ICP in patients with tSAH

<table>
<thead>
<tr>
<th>Variables</th>
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<tr>
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<td>-0.32</td>
<td>0.46</td>
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DISCUSSION

In this study, we found that the AVP levels in plasma and CSF were significantly increased in tSAH patients, and AVP in GCS ≤ 8 group was significantly higher than that in GCS>8 group, although neither plasma AVP nor CSF AVP had statistically significant correlation with GCS. The increase of ICP was more evident in GCS≤8 group, together with high correlation between plasma AVP and ICP. These data indicated the pathophysiological role of AVP in tSAH.

AVP, especially AVP secreted by the hypothalamo-neurohypophyseal system, might act as a neurohumoral factor and is involved in brain injury paradigms, including SAH6,7 and TBI.8 Our early study found that AVP level was elevated in serum 24 hours after TBI and higher in patients with severe injuries than in patients with moderate injuries.4 GCS could be used as an early predictor for tSAH patients. The lower score of GCS at admission adumbrated a poorer prognosis in tSAH patients, which suggested a severe injury in the head.9,10 Our findings also showed that AVP levels in plasma and CSF increased in the early stage of tSAH.

Vasospasm is one of the most critical complications, which contributes to the high morbidity and mortality associated with SAH, as well as the bad outcomes.11 Other study found that the initial GCS score was inversely related to the development of post-traumatic vasospasm but in most cases the period of vasospasm was short and clinical deterioration was rare.12 The complex mechanism of this arterial narrowing is not yet fully understood.13 The existence of extrahypophyseal vasopressinergic pathways within the brain has been found and may allow for independent release and functioning of central AVP vs systemic AVP.14 AVP caused vasoconstriction and intracisternal injection of AVP determined acute vasospasm with a time course similar to the phenomena that seen in normal rats after SAH.15,16 But other research did not support the hypothesis that vasospasm and delayed ischemia were responsible for the poor outcome in tSAH patients.17 In our study, inverse correlation between plasma AVP, CSF AVP and GCS score was not statistically significant and no significant correlation between CSF AVP level and GCS score was found. The limitation was that the degree of cerebral vasospasm was not explored. So it could not be confirmed that AVP is a specific biomarker or plays a key role by aggravating cerebral vasospasm in the pathophysiology of tSAH. Further researches are needed to explore the role of AVP and the relationship between AVP and cerebral vasospasm in the patients with tSAH.

Increase of AVP concentration in the early stage of SAH is of pathogenetic significance in the development of brain edema.7 The high plasma AVP level in tSAH may promote the formation and development of brain edema and secondary cerebral infarction. ICP monitoring has become common practice in the management of many neurologic disorders.18 ICP data are also strong predictors of clinical outcome. Patients with normal ICP showed the best prognosis, whereas patients with increased but controllable ICP did worse and patients with uncontrollable ICP did the worst. In our study, most cases (17/21) had intracranial hypertension. ICP in GCS>8 group was higher than that in GCS≤8 group. A statistically significant correlation was found between the CSF AVP level and ICP, but no remarkable correla-
tion was found between the plasma AVP level and ICP, although there was significant correlation between the plasma AVP and CSF AVP levels. The elevated AVP level, especially the CSF AVP level, may indicate the severe brain damage and deterioration of the conditions. The cerebral AVP may play an important role in the progress of intracranial hypertension and brain edema.

In conclusion, our preliminary study found that plasma AVP levels are elevated after tSAH. The increase of plasma AVP and CSF AVP concentrations in the early stage is related to the severity of brain injury. AVP may play an important role in the pathophysiological process of cerebral vasospasm, brain edema and secondary cerebral infarction. Further study on the precise mechanisms of the role of AVP and clinical significance of agents that attenuate its release following tSAH is required.

**REFERENCES**


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