Norepinephrine in cerebrospinal fluid of patients with cerebral vasospasm

TAKU SHIGENO, M.D.
Department of Neurosurgery, Faculty of Medicine, University of Tokyo, Tokyo, Japan

The content of norepinephrine (NE) in the ventricular, basal cisternal, and lumbar cerebrospinal fluid (CSF) was determined in 19 patients with ruptured cerebral aneurysms at different intervals according to the presence or absence of vasospasm. Twelve were operated on within 3 days after subarachnoid hemorrhage (SAH), prior to the occurrence of vasospasm. Postoperatively, CSF was continuously drained from a basal cistern or lateral ventricle. Norepinephrine was assayed by the highly sensitive automated fluorometric method. The concentration of NE increased in all sites of CSF sampling along with the appearance of vasospasm. Above all, the cisternal CSF of patients with vasospasm contained significantly higher NE (0.246 ± 0.049 ng/ml, mean ± SEM) compared to those without vasospasm (0.075 ± 0.001 ng/ml) (p < 0.001). However, since this increase cannot be considered to be high enough locally to constrict cerebral arteries, this might be only a secondary phenomenon due to release of NE into CSF from various sources in the brain.

KEY WORDS
• cerebral aneurysm • early surgery • vasospasm • norepinephrine • cerebrospinal fluid

It is now widely accepted that subarachnoid blood clots following aneurysm rupture play a major role in the development of vasospasm. Early surgery with extensive removal of subarachnoid blood clots prior to the occurrence of vasospasm may assist in the prevention of vasospasm. However, exact mechanisms to explain vasospasm have not yet been determined and are believed to be multifactorial. One of those factors, norepinephrine (NE), is still considered to be a responsible agent, particularly related to sympathetic nervous system activity. The concentration of NE in cerebrospinal fluid (CSF) from patients with vasospasm has been briefly reported by Cummins and Lothian.

The present report is the first study with measurements of NE in CSF obtained from the basal cisterns in patients with vasospasm who underwent early surgery. The possible participation of NE in vasospasm will be discussed in relation to sympathetic nervous system activity in the acute stage of subarachnoid hemorrhage (SAH).

Clinical Material and Methods

Source and Method of CSF Sampling

Nineteen patients who were subjected to direct operation for a ruptured cerebral aneurysm were selected for this study, with particular reference to the presence of vasospasm (Fig. 1). Of these patients, 12 were operated on within 3 days after SAH, prior to the occurrence of vasospasm. Most treated patients were in Grade II or III according to Hunt's classification, and some were in Grade IV, particularly those with intracerebral hematomas. At the time of surgery, subarachnoid blood clots were removed as completely as possible. Although postoperative vasospasm was observed angiographically in 10 patients, there was a tendency for the vasospasm to be less severe, such as local or multisegmental, according to the classification by Saito, et al. In cases of early surgery, CSF was continuously drained for several days following surgery, through a catheter placed in the basal cistern. When the intracranial pressure was above 15 mm Hg, continuous drainage of ventricular CSF was performed. For the measurement of catecholamines (CA), ventricular, basal cisternal, and lumbar CSF was collected in all of these patients at different times according to the presence or absence of vasospasm. Presence of vasospasm was confirmed angiographically in relation to all CSF samplings.

Method of Catecholamine Measurement

Concentrations of CA, particularly NE and epi-
CSF norepinephrine in cerebral vasospasm

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Days after SAH</th>
<th>2 weeks or more</th>
<th>Type of vasospasm</th>
<th>Grade</th>
<th>Outcome</th>
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<tr>
<td>1. 63M</td>
<td>ICA-PCoA</td>
<td>63</td>
<td>M</td>
<td>1</td>
<td>2</td>
<td>IV</td>
<td>Fair</td>
<td></td>
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<tr>
<td>2. 38M</td>
<td>MCA</td>
<td>38</td>
<td>M</td>
<td>3</td>
<td>2</td>
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<td>Good</td>
<td></td>
</tr>
<tr>
<td>3. 38M</td>
<td>MCA</td>
<td>38</td>
<td>M</td>
<td>7</td>
<td>2</td>
<td>IV</td>
<td>Poor</td>
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<td>68</td>
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<td>Fair</td>
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<tr>
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<td>M</td>
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<td>3</td>
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<td>ACoA</td>
<td>60</td>
<td>M</td>
<td>14</td>
<td>1</td>
<td>IV</td>
<td>Died</td>
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<td>ICA-PCoA</td>
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<td>M</td>
<td>14</td>
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**Fig. 1.** Summary of clinical course in 19 patients with a ruptured cerebral aneurysm and record of cerebrospinal fluid sampling for measurement of catecholamine concentrations. Locations of the aneurysm: ICA = internal carotid artery; PCoA = posterior communicating artery; MCA = middle cerebral artery; ACoA = anterior communicating artery; A-2 = portion of the anterior cerebral artery. Type of vasospasm: 0 = absent; 1 = diffuse; 2 = multisegmental; 3 = local. Neurological grade was determined by Hunt's system at the time of aneurysm surgery.

Norepinephrine and epinephrine were clearly separated, and the sensitivity was considered to be in the order of 1 pg/ml for NE when 5 ml of CSF was used for single measurement (Fig. 3). The constant recovery ratio for NE was 71.5 ± 1.2% (mean ± SD for 10 samples). All CSF samples contained enough NE for detection, whereas epinephrine could rarely be detected, irrespective of the presence or absence of vasospasm.

**Concentration of NE in CSF**

In all three sites of CSF sampling, the concentration of NE increased with the appearance of vasospasm, beginning 4 days after SAH (Fig. 4). This increase was more marked in the cisternal CSF, particularly between Days 4 and 7 of the illness. When the values of NE were pooled according to the site of CSF sampling over the whole period of the illness, the cisternal CSF contained significantly higher NE in the presence of vasospasm (0.246 ± 0.049 ng/ml (mean ± SE) for eight samples, p < 0.001) compared to the values without vasospasm (0.075 ± 0.011 ng/ml for eight samples). This increase was about threefold, and corresponded to the order of 10^-9 in molar concentration.

**Results**

**Sensitivity of Catecholamine Measurement**

Norepinephrine and epinephrine were clearly separated, and the sensitivity was considered to be in the order of 1 pg/ml for NE when 5 ml of CSF was used for single measurement (Fig. 3). The constant recovery ratio for NE was 71.5 ± 1.2% (mean ± SD for 10 samples). All CSF samples contained enough NE for detection, whereas epinephrine could rarely be detected, irrespective of the presence or absence of vasospasm.

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Discussion

There is evidence that cerebral vasospasm is one of the most important factors affecting the prognosis of patients in the acute stage of SAH.23-25 Recent computerized tomographic studies in the very early period after SAH have revealed that there is a close relationship between the presence of subarachnoid blood clots and subsequent development of vasospasm.23-25 In cases of early surgery with extensive removal of subarachnoid blood clots and subsequent drainage of bloody cisternal CSF, the progression of vasospasm might be partly prevented, as shown in the present study as well as in previous reports.23,25

Although many vasoactive substances have been proposed as a pathogenetic factor in the development of vasospasm, NE may be one of those causative agents, being related to sympathetic nervous system activity. It has been reported that adrenergic overactivity occurs in the acute stage of SAH. Indirect evidence, such as systolic hypertension24,25 and electrocardiographic changes34 (presumably due to an increase of plasma NE concentration), has been documented. In contrast, there is little direct evidence, except for measurement of CA in urine, plasma, and lumbar CSF from patients with SAH. Neil-Dwyer, et al.,19 observed a high urinary excretion of CA in patients with vasospasm, which persisted for more than 2 weeks. Peerless and Griffiths21 disclosed a significant increase of plasma NE several days after SAH, which was closely related to the severity of SAH; they concluded that NE might be responsible for the development of vasospasm. Cummins and Lothian6 measured CA in lumbar CSF obtained from patients with vasospasm, and revealed a close relationship between the NE content and the severity of vasospasm. Nevertheless, the values reported by these authors were only on the order of 10⁻⁸M of NE, which was too low to bring about significant cerebral arterial contraction. Cerebral arteries are known to be less responsive to NE than are peripheral arteries. From many in vitro studies using isolated cerebral arteries,4,30 the median effective dose (ED₅₀) has been reported to be on the order of about 10⁻⁶M. Also from in vivo studies with an application of NE on pial arteries or arterioles, Wahl, et al.,32 and Wei, et al.,33 reported that significant contraction was observed above the concentration of 10⁻⁶M.

Until recently, there has been no report on the concentration of NE in the basal cisternal CSF circulating around the circle of Willis. Using the cisternal catheter in cases of early surgery, it was possible to
measure the content of NE in the cisternal CSF with the aid of a highly sensitive automated fluorometric method. It was shown that the NE content of the cisternal CSF was higher than in the ventricular and lumbar CSF in the presence of vasospasm. However, the concentration still remained on the order of $10^{-9}$M. Therefore, it is questionable if such a slight increase of NE present locally around the spastic artery causes vasospasm or is merely a result of SAH.

Several sources of NE in CSF seem to exist in the brain, which can explain the increase in SAH and vasospasm. First, NE may be derived from neurons of the brain. It has been known that NE is present in relatively large concentrations in various parts of the brain, including the hypothalamus. Fluorescent histochemical study has shown that there is an ascending noradrenergic pathway from the brain stem to the hippocampus and cerebral cortex. In cerebral ischemia, NE in the brain tissue has been reported to decrease following its generalized release from presynaptic terminals throughout the brain. Meyer, et al., reported a series of patients with recent cerebral infarction or hemorrhage who showed an elevated level of NE in lumbar CSF; the release of NE into the CSF of these patients can be explained by this mechanism. Since there is similar anoxic ischemic cerebral damage in cases of SAH and vasospasm, an increase of NE in CSF can also be expected. Furthermore, frequent ischemic lesions of the hypothalamus in patients with SAH can explain the greater increase of NE in the cisternal CSF.

The second source of NE in CSF could be a release of NE from nerve terminals on cerebral vessels. There is general agreement that subarachnoid arteries are richly innervated from the superior cervical ganglion, and contain more NE than the peripheral arteries. It has been documented that SAH causes disappearance of NE fluorescence of the perivascular adrenergic plexus in a few days. Along with this fact, the so-called denervation hypersensitivity seems to be a causative factor in vasospasm, whereas it is still speculative or only partly documented in in vitro studies.

A third source might be circulating NE, which has been reported to increase with the presence of vasospasm as a reflection of generalized sympathetic over-
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activity, and can enter into CSF through a damaged blood-brain barrier. In normal circumstances, NE cannot cross the blood-brain barrier.\textsuperscript{16,20} In SAH, however, disturbances of the blood-brain barrier have been reported to occur,\textsuperscript{8,27} which allow the release of plasma NE into CSF.

Although the role of increased NE in CSF (particularly in the basal cistern) is still unclear, it could be caused by a secondary release of NE through above-mentioned possible routes.

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References


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FIG. 4. Norepinephrine concentration in the cerebrospinal fluid (CSF). Squares = ventricular CSF; circles = cisternal CSF; triangles = lumbar CSF; white symbols = without spasm; black symbols = with spasm. Left: Changes in relation to days after subarachnoid hemorrhage. Right: Pooled values in relation to the site of CSF sampling.
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Address reprint requests to: Taku Shigeno, M.D., Department of Neurosurgery, University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan.