Brain monoamine metabolites and tryptophan in ventricular CSF of patients with spasm after aneurysm surgery

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Intraventricular pressure was followed continuously after operation for intracranial arterial aneurysm in 20 patients. Ventricular cerebrospinal fluid (CSF), homovanillic acid (HVA), tryptophan, and 5-hydroxyindole acetic acid (5-HIAA) were analyzed daily for 5 days, beginning before the clipping of the aneurysm. Postoperatively, seven patients had spasm, verified clinically and angiographically. Seven other patients with no clinical or angiographic signs of spasm, hydrocephalus, or increased intracranial pressure (ICP) served as controls. Nine of the 20 patients were hydrocephalic.

The mean ± SE values of HVA, tryptophan, and 5-HIAA in the controls were 264 ± 40, 1116 ± 85, and 88 ± 8 ng/ml, respectively, in the controls, and 182 ± 20, 982 ± 89, and 78 ± 3 ng/ml, respectively, in the patients with spasm. The differences are not statistically significant. However, the low values of HVA may have been produced by ischemic changes caused by the spasm. In hydrocephalic patients ventricular CSF tryptophan levels were statistically significantly higher, and 5-HIAA levels lower than in controls. In patients with increased ICP, neither alterations nor intercorrelations of monoamine metabolites and tryptophan were found. The results do not give direct support to prophylactic neuropharmacological treatment of postoperative arterial cerebral spasm. However, ventricular HVA, tryptophan, and 5-HIAA measurements can be used for prognostic purposes during the first few days after the operation.

Key Words • aneurysm • cerebral arterial spasm • monoamine metabolites • tryptophan • subarachnoid hemorrhage • ventricular CSF

The most unsolved problem in the treatment of intracranial arterial aneurysms is prolonged arterial spasm, which often accompanies existing subarachnoid hemorrhage (SAH) as well as the surgical manipulation of the aneurysm. Clinical and experimental data suggest that spasm is caused by vasoactive substances in the cerebrospinal fluid (CSF); CSF taken from patients with cerebral arterial spasm after SAH contains substances that contract the isolated human basilar artery. Other authors have previously suggested that substances like biogenic amines, histamine, and prostaglandin may be responsible for cerebral arterial vasoconstriction, which could be prevented by adequate neuropharmacological treatment. Starling, et al. have
demonstrated human serum potentiated contrac
tile responses to serotonin and nor-

 Recent studies indicate that cerebral hypoxia is related to biogenic amine metabolism in experimental animals. Transient ischemia suppresses brain tryptophan levels and indolamine synthesis. Experimental hypoxia or experimental vascular occlusion reduce brain monoamine synthesis and metabolism. These data support the contention that brain monoamines play an important role in the progression of cerebral infarction, proposed earlier by Welch, et al. An inappropriate loss of monoamines in the ischemic area may be an active factor in the progressive reduction of cerebral blood flow and contribute to the progression of infarction.

There have been few studies devoted to the possible role of brain monoamines in clinical stroke and none to their role in prolonged spasm. Elevated levels of noradrenaline and serotonin have been measured in the lumbar CSF of patients with cerebral infarction, and increased levels of 5-hydroxyindole acetic acid (5-HIAA), an end product of serotonin metabolism, have been found in the lumbar CSF several days after SAH. The concentration of homovanillic acid (HVA), the main metabolite of brain dopamine, and of 5-HIAA are generally supposed to reflect the metabolism of their parent monoamines. Tryptophan is the natural precursor of serotonin in the body, and CSF tryptophan has been related to brain tryptophan concentrations. The aim of the present study was to analyze these monoamine metabolites from the ventricular CSF of patients during routine postoperative intraventricular pressure recording after aneurysm surgery. The levels of the metabolites were correlated to the possible spasm (with relative hypoxia) in the later clinical course as well as to the role of increased intracranial pressure (ICP) and hydrocephalus of the patients.

Clinical Material and Methods

Summary of Patients

The study involved 20 consecutive patients who underwent intracranial aneurysm surgery in the Division of Neurosurgery, University Central Hospital, Turku, between November 15, 1975, and May 31, 1976. The mean age in the group was 43 years; eight of the 20 patients were women. All had had at least one verified SAH; seven patients had had two bleeding episodes and one had three episodes preoperatively. The longest time from the last hemorrhage to the operation was 3 weeks, mean 14 days. Nine patients were below Grade II in Botterell's classification at the time of operation. None of the patients had clinical and angiographic signs of active spasm at the time of operation.

In all 20 patients the aneurysm was ligated with a clip, using controlled hypotension with nitroprusside, hyperventilation, and micro-surgical technique. The intracranial pressure was recorded through a catheter in one lateral ventricle inserted at the beginning of the operation. The recording was continued for at least 2 days after the operation, at which time the control angiography was performed. A standard pressure-recording system with a Statham transducer, Olli-tuote amplifier, and Honeywell recorder was used. If the pressure remained steadily below 15 mm Hg, it was regarded as normal.

The aneurysms were located in the anterior communicating or pericallosal area in 11 patients, in the internal carotid area in seven, and in the medial cerebral branch in two patients. Three patients had multiple aneurysm; in one patient both of the aneurysms were ligated.

The spasm and hydrocephalus were evaluated by angiography performed preoperatively and on the second day postoperatively. In nine patients there was definite evidence of hydrocephalus either before or just after the operation; four of these patients needed a shunt. In seven patients spasm was verified at angiography. Spasm was asymptomatic in only one patient; all the others had transient neurological signs. All the patients underwent routine dexamethasone treatment during the operative period.

*Statham transducer manufactured by Statham Laboratories, Inc., P.O. Box 1178, Hato Rey, Puerto Rico.
†Amplifier manufactured by Olli-Tuote Co., SF 02320, Kivenlahti, Finland.
‡Low-speed recorder manufactured by Honeywell Information Systems, 200 Smith Street, Waltham, Massachusetts.
TABLE I
Effects of cerebral arterial spasm and hydrocephalus on the ventricular levels of HVA,
tryptophan, and 5-HIAA in 20 patients after aneurysm surgery*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>HVA</th>
<th>Tryptophan</th>
<th>5-HIAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>264 ± 40 (17)</td>
<td>1116 ± 85 (19)</td>
<td>88 ± 8 (24)</td>
</tr>
<tr>
<td>spasm</td>
<td>182 ± 20 (20)</td>
<td>982 ± 89 (19)</td>
<td>78 ± 3 (25)</td>
</tr>
<tr>
<td>hydrocephalus</td>
<td>202 ± 28 (24)</td>
<td>1321 ± 120 (19)†</td>
<td>76 ± 6 (29)‡</td>
</tr>
</tbody>
</table>

*Number of samples is given in parentheses and concentrations are expressed in ng/ml ± SEM. HVA = homovanillic acid; 5-HIAA = 5-hydroxyindole acetic acid.
†Statistically significant difference from control group: p < 0.05. Mann-Whitney U-test.
‡Statistically significant difference from control group: p < 0.005. Mann-Whitney U-test.

There was one death in this series from acute pulmonary thromboembolism on the second postoperative day. After at least 6 months of follow-up review, 14 patients are doing well and are engaged in active work, three others are at home with minor sequelae but still unable to return to work, and two patients need institutional care. Both of the latter had organic psychosyndromes preoperatively with hydrocephalus and spasm.

Chemical Analyses

The first ventricular sample was collected at the beginning of the operation, when the catheter was first inserted into the lateral ventricle. Daily samples were taken through a stopcock as long as the pressure recording was continued, until at least 2 days after the operation. The samples, usually 10 to 20 cc, were immediately centrifuged at 800 G for 15 minutes and then kept frozen at -25°C until analyzed. Samples contaminated with blood were discarded because of the presence of tryptophan in blood. We also found that xanthochromia disturbed the fluorometric determination of HVA. Assays of HVA, 5-HIAA, and tryptophan were performed by the methods generally used in our laboratory.

Statistical methods included linear regression with correlation coefficients and the Mann-Whitney test.

Results

In seven of 20 patients no clinical or radiological signs of spasm or hydrocephalus were found, and their ICP was also normal throughout the recording. These patients were regarded as controls. Ventricular levels of CSF HVA, tryptophan, and 5-HIAA of control patients were 264 ± 40 ng/ml, 1116 ± 85 ng/ml, and 88 ± 8 ng/ml (mean ± SE), respectively. Cerebral arterial spasm was found in seven patients, and among them only one patient had no clinical symptoms. Hydrocephalus was demonstrated in three patients with spasm and in six patients without spasm. Intracranial pressure was increased in five patients with spasm and in four patients with hydrocephalus. Postoperative ventricular CSF levels of HVA, tryptophan, and 5-HIAA did not differ statistically significantly from the preoperative levels within each group, and no variation between postoperative days was noticed.

Table 1 shows that cerebral arterial spasm does not cause a statistically significant alteration in the levels of measured metabolites, although a tendency toward reduced values can be seen, especially in the HVA samples. This tendency was confirmed by the finding that in the only patient with spasm who did not show any clinical symptoms the mean value of HVA was very close to that of the controls (275 ± 37 ng/ml).

Raised ICP was not associated with altered monoamine metabolite concentrations during

TABLE 2
Effects of ICP on the ventricular CSF levels of HVA, tryptophan, and 5-HIAA in 20 patients after aneurysm surgery*

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Pressure</th>
<th>High Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVA</td>
<td>264 ± 40 (17)</td>
<td>204 ± 22 (20)</td>
</tr>
<tr>
<td>tryptophan</td>
<td>1116 ± 85 (19)</td>
<td>1109 ± 123 (16)</td>
</tr>
<tr>
<td>5-HIAA</td>
<td>88 ± 8 (24)</td>
<td>79 ± 5 (23)</td>
</tr>
</tbody>
</table>

*No statistically significant differences are seen between groups. Values are given in ng/ml, mean ± SE, and the number of samples in parentheses. Mann-Whitney U-test. ICP = intracranial pressure; CSF = cerebrospinal fluid; HVA = homovanillic acid; 5-HIAA = 5-hydroxyindole acetic acid.
TABLE 3
Correlation coefficients between ventricular CSF levels of HVA, tryptophan, and 5-HIAA in patients after aneurysm surgery*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>HVA vs 5-HIAA</th>
<th>Tryptophan vs 5-HIAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>+0.22</td>
<td>+0.48§</td>
</tr>
<tr>
<td>spasm</td>
<td>+0.14</td>
<td>-0.17</td>
</tr>
<tr>
<td>hydrocephalus</td>
<td>+0.72†</td>
<td>-0.58‡</td>
</tr>
<tr>
<td>all groups</td>
<td>+0.43‡</td>
<td>-0.18</td>
</tr>
</tbody>
</table>

*CSF = cerebrospinal fluid; HVA = homovanillic acid; 5-HIAA = 5-hydroxyindole acetic acid.
†Statistical significance: p <0.001.
‡Statistical significance: p <0.01.
§Statistical significance: p <0.05.

the first 4 days after surgery (Table 2). On the contrary, hydrocephalus was associated with statistically significant alterations in the concentrations of tryptophan and 5-HIAA from control values (Table 1).

Correlations between variables were calculated separately for control, spasm, hydrocephalus, and for the whole material. Ventricular CSF concentrations of HVA were positively correlated with 5-HIAA in the total material and in patients with hydrocephalus (Table 3). A positive correlation was noticed between tryptophan and 5-HIAA in control patients, and a statistically significant negative correlation between the same variables was seen in the hydrocephalic patients (Table 3). In patients with increased ICP no intercorrelations were found (HVA vs 5-HIAA, r = 0.228; tryptophan vs 5-HIAA, r = 0.263).

Discussion

In the present study ventricular CSF levels of HVA, tryptophan, and 5-HIAA seemed to be reduced in connection with cerebral arterial spasm after SAH. However, this reduction did not reach the level of statistical significance. The reduction of HVA levels correlates with the presence of neurological symptoms. Hydrocephalus was associated with reduced ventricular CSF concentrations of 5-HIAA and elevated tryptophan concentrations relative to control levels. Increased ICP was not associated with monoamine metabolite and tryptophan levels in ventricular CSF. This is in accordance with other recent findings. The pressure was never very high, never over 35 mm Hg, in our study.

Experimental cerebral ischemia causes profound depletion of ipsilateral brain dopamine and its deaminated metabolites, including HVA, in monkeys, Mongolian gerbils, and rats. In a very recent study, precursors and metabolites of serotonin and dopamine were determined in the ventricular CSF of psychiatric patients. Controls included 12 neurological patients divided into two subgroups: one with abnormal CSF flow, and the other without any indications of abnormal CSF flow. Interestingly, four patients in the latter group were undergoing surgery for cerebral aneurysm after suffering SAH. The concentration of ventricular CSF HVA was significantly reduced in the SAH group.

In the present clinical study, the ventricular CSF levels of HVA were moderately decreased in patients with spasm. This may be explained by the assumption that the spasm produced regional hypoxia in the brain. Clinical signs of ischemia were noted in six of seven patients with spasm. The one patient who had no neurological symptoms after the operation had normal levels of ventricular CSF HVA. Thus, ventricular CSF HVA measurements may have some prognostic value during the first few days after operation for cerebral arterial aneurysm.

Experimental cerebral ischemia causes a significant increase in brain tryptophan, and transient ischemia in the rat produces a statistically significant decrease of brain tryptophan followed by an increase during re-circulation. In the present study ventricular tryptophan levels were not statistically significantly altered by cerebral arterial spasm, although some reduced values were found when compared with values from patients without spasm. Among the very few reports concerning ventricular tryptophan levels in neurological patients, high mean concentrations (1620 ng/ml) have been found in patients with brain-tissue damage, and a lower mean value of tryptophan was detected in patients undergoing surgery (860 ng/ml). In the present study increased tryptophan levels were found in patients with hydrocephalus, but elevated ICP was not associated with a change in tryptophan levels. Ventricular CSF tryptophan levels very probably are parallel with the concentration of brain tryptophan. Thus, an increased level of ventricular CSF tryptophan in hydrocephalic patients reflects increased brain tryptophan,
and decreased tryptophan levels found in patients with spasm reflects decreased brain tryptophan concentrations.

Indolamine synthesis and metabolism is also reduced by cerebral ischemia in experimental animals, but transient hypoxia did not alter brain 5-HIAA levels in the rat, and they were elevated after restitution in Mongolian gerbils. In the present clinical study, 5-HIAA levels of patients with cerebral arterial spasm were not statistically significantly reduced. In patients with hydrocephalus low ventricular CSF concentrations of 5-HIAA differed statistically from control values. Since low 5-HIAA and high tryptophan levels are seen simultaneously with a significant inverse correlation, it appears likely that serotonin synthesis and metabolism are impaired in the hydrocephalic brain. Increased ventricular 5-HIAA levels, however, were seen by West, et al., in patients with increased ICP and obstructive hydrocephalus. In another study, ventricular 5-HIAA levels were reduced in patients with communicating hydrocephalus and without increased ICP.

Brain monoamine metabolites and tryptophan are altered in patients who are operated on for intracranial aneurysm and who suffer from neurological complications. Cerebral arterial spasm seems to cause a relative reduction of monoamine metabolite concentrations, probably based on its hypoxic effect on brain tissue. Since the hypoxia is regionally dependent on the impaired arterial supply, regional alterations of monoamine metabolism are difficult to detect from our measurements of ventricular CSF. A combination of increased ICP with hydrocephalus, as shown in an earlier series and again in this study, may activate the spasm by transmural pressure changes as shown in in vitro studies. Hydrocephalus per se seems to be correlated with impaired serotonin synthesis and metabolism under these circumstances.

In spite of these changes, our results at this stage do not give much support to recent proposals for the utilization of preventive neuropharmacological treatment of postoperative spasm.

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References

CSF monoamine metabolites and postoperative spasm


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