CSF Serotonin Concentrations and Cerebral Arterial Spasm in Patients with Ruptured Intracranial Aneurysm

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SUMMARY In 26 patients with recent rupture of an intracranial sacular aneurysm the CSF concentrations of serotonin (5-HT) were measured repeatedly by a radioimmunoassay. The 5-HT level in ventricular CSF collected between the 2nd and 15th day after SAH ranged between $<2$ and $5 \text{ nmol/L.}$ These did not differ from the levels found in the ventricular CSF ($<2-3 \text{ nmol/L})$ and lumbar CSF ($<2-3 \text{ nmol/L})$ of control patients. 5-HT concentrations did not correlate with the severity of angiographical vasospasm, nor with CSF pressure or clinical grade. In two patients with severe postoperative vasospasm, however, cisternal CSF collected during operation and contaminated by fresh blood showed 5-HT concentrations exceeding $25 \text{ nmol/L.}$ Thus, although these results do not support the conception that 5-HT plays a major role in sustaining delayed vasospasm, they suggest that 5-HT liberated from platelets may be operative in the initiation of cerebral arterial spasm.

These inconsistent results have not been clarified by human studies. Althoug elevated levels of 5-HT in cerebrospinal fluid (CSF) from patients with various cerebrovascular diseases have been reported, the risk of measuring closely related indoles in CSF instead of 5-HT with insensitive or nonspecific methods has been stressed.

In the present study we used a specific and highly sensitive radioimmunoassay for the determination of 5-HT in CSF. The purpose of this investigation was to obtain information of the concentration of 5-HT in CSF of patients with SAH, and to study the relation between 5-HT and cerebral vasospasm.

**Clinical Series**

The series studied included 26 patients (13 women and 13 men) with recent rupture of an intracranial sacular aneurysm, admitted to the Department of Neurosurgery in Aarhus between April 1980 and February 1981. The mean age of the patients was 50 years (range 27-72). The clinical condition of the patients was assessed daily and graded according to the system of Hunt and Hess. Cerebral angiography was performed in all patients between the 1st and 7th day after the initial bleeding and was repeated in 10 patients postoperatively. The degree of vasospasm was measured on angiograms and defined as follows: a reduction in arterial diameter of less than 25% was no

PERSISTENT CONSTRICTION of the major cerebral arteries is a common phenomenon in patients with subarachnoid hemorrhage (SAH). The deleterious cerebral ischemia that accompanies severe vasospasm significantly increases the mortality and morbidity in patients with ruptured intracranial aneurysm.

However, the etiology of cerebral vasospasm remains obscure, and no satisfactory treatment has yet been devised.

Serotonin, or 5-hydroxytryptamine (5-HT), is a potent vasoconstrictor which has been implicated in the etiology of cerebral vasospasm following aneurysm rupture. Our knowledge of the possible role of 5-HT in vasospasm has mainly been achieved by experimental work. In 1961 Raynor, McMurtry, and Pool demonstrated that 5-HT applied to the cerebral cortex of the cat caused spasm of the pial vessels. Since then, several studies have pointed to 5-HT as a causative agent. It has been proposed that the sustained release of 5-HT from shed blood platelets in the subarachnoid space is responsible for the prolonged arterial constriction. Other investigations do not support the conception that 5-HT plays a major role in the production of vasospasm.

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spasm, between 25% and 50% slight spasm, and a reduction of 50% or more severe spasm.

Continuous monitoring of the intraventricular pressure (IVP) according to the method of Lundberg25 was performed in 19 patients for an average period of 6 days following admission (between the 2nd and 15th day after SAH). Ventricular CSF for determination of 5-HT was withdrawn from the ventricular catheter close to the patient's head after 2 ml of CSF had been allowed to escape. CSF was preferably sampled when pressure monitoring was started, on the day of angiography, and when changes in clinical condition occurred. An average of 3 samples (1-8) was collected per patient. In two patients only one sample was obtained because of clogging of the ventricular catheter.

Cisternal CSF was obtained from the immediate environment of the ruptured aneurysm during operation in 10 patients including 3 from the above-mentioned group.

Control Series

As control group, a series of 10 patients with normal pressure hydrocephalus, subjected to measurement of IVP and isotope ventriculo-cisternography, was studied. One sample of ventricular CSF per patient was collected during these procedures. In addition, samples of lumbar CSF from 21 patients undergoing myelography were collected. In both control groups samples with blood admixture were discarded.

Determination of CSF 5-HT

A total of 100 CSF samples was analysed. Two ml of CSF were collected in a test tube containing 100 µl of a solution containing 250 µmol/l chlorimipramine, 250 µmol/l clorgyline, and 250 µmol/l pargyline, and immediately cooled in an ice bath. After centrifugation for 30 minutes at 2200 rpm. (1500 g) the supernatant was separated and stored at −20°C for 2 to 3 weeks before analysis by radioimmunoassay.

The minimum detectable concentration of 5-HT was found to be 2 nmol/l by this method.

Determination of CSF Blood Admixture

The content of 5-HT in serum originates in platelets, and in normal man the serum 5-HT concentration is 380-900 nmol/l (mean 600 nmol/l). In order to assess the relation between the degree of blood admixture to CSF and the CSF 5-HT concentrations measured in this study, we determined the concentration of free hemoglobin by a diphenylamine-method in all hemorrhagic CSF samples. The average concentration of hemoglobin in blood was assumed to be 10 mmol/l. Thus, a concentration of free hemoglobin of 0.1 mmol/l equals an admixture of whole blood to CSF of 1%.

Results

In table 1 the results of CSF 5-HT determinations in aneurysm patients and in control patients are shown. 5-HT concentrations of ventricular CSF in 19 aneurysm patients were all very low, 2/3 being less than 2 nmol/l. The degree of blood admixture to CSF (0-9%) did not correlate with the 5-HT concentrations in ventricular CSF. The 5-HT levels of the two control groups, being about 2 nmol/l, did not differ from those found in ventricular CSF and in the majority of cisternal CSF of aneurysm patients.

On admission, the clinical grade of the 19 patients was as follows: 3 grade II (16%), 11 grade III (58%), and 5 grade IV (26%). During the period of study 4 improved (21%), 8 remained unchanged (42%), and 7 deteriorated (37%). Serial measurements in individual patients showed that clinical changes were not accompanied by changes in 5-HT concentrations. In particular, no increase in 5-HT was observed concomitantly with deterioration. There was no difference between 5-HT in the alert and the comatose patients.

The IVP level was normal in 2 patients (0-10 mm Hg), slightly elevated in 5 (10-20 mm Hg), moderately elevated in 11 (20-40 mm Hg), and severely increased in 1 (> 41 mm Hg). Again, the 5-HT concentration of more than 2/3 of CSF samples was 2 nmol/l or less irrespective of the IVP level measured immediately before collection. The highest 5-HT concentration measured of 4 and 5 nmol/l were withdrawn at IVP values of 29 and 25 mm Hg, respectively. On the other hand, 4 samples collected at pressures above 40 mm Hg contained less than 2 nmol/l.

Measurement of angiographical vasospasm showed no spasm in 7 patients, slight spasm in 5, and severe spasm in 7. Figure 1 shows the relation between ventricular CSF 5-HT concentrations and cerebral vasospasm in 17 out of 19 patients. In 2 patients CSF was not sampled in close relation to angiography. All values were below 5 nmol/l and no differences among degrees of spasm were disclosed. Repeated sampling of CSF showed that small 5-HT changes observed in individual patients did not correlate with the development of spasm.

Figure 1 also shows the 5-HT concentrations of cisternal CSF collected during aneurysm surgery in 10 patients. Two patients who postoperatively developed severe spasm had the highest 5-HT concentrations measured in this study. In table 2 the 5-HT concentrations and clinical data of all 10 patients are shown. Obviously, the highest 5-HT concentrations were seen only in CSF which was severely contaminated with fresh blood during the exposure of the basal cisterns and the aneurysm. A 6-7% admixture of blood to CSF in 2 patients was associated with 5-HT values above 25 nmol/l, while an admixture of less than 2% in the

<table>
<thead>
<tr>
<th>Table 1. CSF Serotonin Concentrations</th>
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<tbody>
<tr>
<td>Category (samples)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Aneurysm:</td>
</tr>
<tr>
<td>Ventricular CSF</td>
</tr>
<tr>
<td>Cisternal CSF</td>
</tr>
<tr>
<td>Control:</td>
</tr>
<tr>
<td>Ventricular CSF</td>
</tr>
<tr>
<td>Lumbar CSF</td>
</tr>
</tbody>
</table>
Rest corresponded with 5-HT concentrations below 10 nmol/l.

Only the 2 aforementioned patients showed severe spasm at postoperative angiography. The time course of events in relation to CSF 5-HT concentrations in one of these patients (case 4) is depicted in figure 2. Angiography performed on day 2 after SAH showed no spasm (fig. 3A) and the ventricular CSF 5-HT level was about 2 nmol/l during the first week. Operation on day 10 was complicated by heavy bleeding during dissection of the aneurysmal sac and marked spasm of the adjacent arteries was observed. CSF was hemorrhagic with a 5-HT concentration of 26 nmol/l. Postoperative angiography 6 days later revealed severe diffuse spasm (fig. 3B). On 6 months' follow-up, the patient was incapacitated by aphasia and a right hemiplegia. CT scan showed a large left fronto-temporal infarction.

**Discussion**

In the present study, ventricular CSF in patients with recent rupture of an intracranial aneurysm contained very small amounts of serotonin (5-HT), about 2 nmol/l. Only minimal changes in 5-HT concentrations were observed during the first 2 weeks following the initial SAH, and they did not correlate with the IVP, the changes in clinical condition, or the severity of cerebral arterial spasm.

5-HT has been implicated frequently in cerebrovascular diseases. However, concerning patients with intracranial aneurysms, only a few investigations exist. Vapalathi et al. found slightly reduced levels of the 5-HT metabolite 5-hydroxyindole acetic acid (5-HIAA) in ventricular CSF of patients with vasospasm. They also measured the concentration of the 5-HT precursor tryptophan, and found this to be decreased probably due to the hypoxic effect of vasospasm on brain tissue. Buckell measured 5-HT concentrations of 57-500 nmol/l in hematoma fluid surrounding the aneurysm in 3 patients with spasm. Allen et al. found the 5-HT concentrations (29-86 nmol/l) in lumbar CSF, taken from 3 patients 2-7 days following SAH, capable of producing a prolonged contraction of the canine basilar artery in vitro.

It has been questioned whether 5-HT is present in sufficient amounts in CSF to be detectable with the methods used hitherto. In the present study, using a radioimmunoassay, barely detectable concentrations were measured in most CSF samples. The only parameter measured which apparently influenced 5-HT concentrations was the admixture of fresh blood to CSF as observed during operation. This might indicate that 5-HT is released immediately from

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, sex</th>
<th>Site of aneurysm</th>
<th>Clinical grade</th>
<th>Postoperative spasm</th>
<th>CSF serotonin nmol/l</th>
<th>Blood admixture to CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>56 F</td>
<td>Int. car.</td>
<td>III</td>
<td>Severe</td>
<td>26</td>
<td>6.5%</td>
</tr>
<tr>
<td>5</td>
<td>57 F</td>
<td>Mid. cer.</td>
<td>II</td>
<td>None</td>
<td>5</td>
<td>n.p.</td>
</tr>
<tr>
<td>9</td>
<td>33 M</td>
<td>Ant. comm.</td>
<td>II</td>
<td>Slight</td>
<td>3</td>
<td>1.8%</td>
</tr>
<tr>
<td>13</td>
<td>38 F</td>
<td>Int. car.</td>
<td>II</td>
<td>None</td>
<td>&lt;2</td>
<td>0.1%</td>
</tr>
<tr>
<td>18</td>
<td>63 F</td>
<td>Int. car.</td>
<td>II</td>
<td>Slight</td>
<td>&lt;2</td>
<td>0.8%</td>
</tr>
<tr>
<td>22</td>
<td>65 F</td>
<td>Int. car.</td>
<td>I</td>
<td>Slight</td>
<td>4</td>
<td>0.3%</td>
</tr>
<tr>
<td>23</td>
<td>56 M</td>
<td>Ant. comm.</td>
<td>II</td>
<td>None</td>
<td>3</td>
<td>0.3%</td>
</tr>
<tr>
<td>24</td>
<td>62 M</td>
<td>Ant. comm.</td>
<td>III</td>
<td>Severe</td>
<td>60</td>
<td>6.8%</td>
</tr>
<tr>
<td>26</td>
<td>33 F</td>
<td>Vertebral</td>
<td>II</td>
<td>None</td>
<td>10</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

**Table 2. Cisternal CSF Serotonin Concentrations and Clinical Data in 10 Patients Undergoing Surgical Repair of Ruptured Intracranial Aneurysm**

Abbreviations: Int. car. = internal carotid artery; Mid. cer. = middle cerebral artery; Ant. comm. = anterior communicating artery; n.p. = not performed (CSF colorless).
Platelets during bleeding into the subarachnoid space. It seems reasonable to assume that the uniformly low 5-HT levels found in both aneurysm and control patients represent a normal 5-HT level in CSF. Thus, the fact that the 5-HT concentrations in "old" hemorrhagic CSF collected 2 days after SAH were normalized might indicate that excess 5-HT rapidly disappears from CSF.

In patients with impaired CSF flow and absorption due to SAH, samples of ventricular CSF probably represent a mixture of cisternal and ventricular CSF. Our results showed almost identical levels of 5-HT in lumbar, cisternal, and ventricular CSF. Thus, a ventricular/lumbar gradient for 5-HT, as has been demonstrated earlier for 5-HIAA, was not found in the present study. The fact that identical 5-HT values were measured in ventricular CSF and in cisternal CSF not contaminated by significant amounts of fresh blood suggests that ventricular CSF reliably reflected cisternal 5-HT concentrations. A remarkable exception to the uniformly low 5-HT levels was the finding of relatively increased

**Figure 2.** Time course of vasospasm and CSF serotonin (5-HT) concentrations in 56-year-old female with ruptured internal carotid aneurysm. Angiography on day 2 after SAH showed no spasm. At operation (OP) marked spasm of the exposed internal carotid artery was observed. Angiography on day 6 postoperatively revealed severe spasm.

**Figure 3.** A: Left internal carotid angiogram demonstrating aneurysm of the internal carotid artery. No spasm is seen. B: Six days after clipping of the aneurysm severe spasm has developed (same patient as fig. 2).
5-HT concentrations in two cisternal CSF samples with considerable admixture of fresh blood.

Allen et al. proposed in 1974 on the basis of in vitro and in vivo experimental work that the concentration of free serotonin in CSF is directly related to cerebral arterial spasm, and that a sustained release of bound 5-HT from platelets in CSF and from the blood clot surrounding the arteries prolongs the spasm for several days.6-8 Our results do not support that hypothesis. Even in patients with severe diffuse spasm 5-HT concentrations often were less than 2 nmol/l and never exceeded 5 nmol/l.

In vitro studies of isolated human cerebral arteries have shown that 5-HT concentrations of 7-90 nmol/l are necessary to produce half maximal contraction while maximal contraction requires concentrations between 500 and 1000 nmol/l.26, 27 We did not find concentrations of 5-HT in ventricular CSF from patients with severe spasm that would cause half maximal contraction in vitro. The vessels of normal animals do not have the same sensitivity to 5-HT as isolated cerebral vessels. In in vivo experiments cisternal injections of 5-HT at 1000 to 10,000 nmol/l produced only moderate spasm lasting 2-3 hours.6 However, in animals previously exposed to SAH, a much stronger contractile effect of 5-HT has been observed.28 SAH in feline cerebral vessels induced a supersensitivity to 5-HT which was most pronounced on the 3rd day after the bleeding and then gradually disappeared.29 Recently a similar increased response to 5-HT in isolated extracranial arteries from aneurysm patients has been demonstrated.30

Even in the presence of presumed arterial supersensitivity to 5-HT in patients with SAH it seems unlikely that the 5-HT concentrations found in the present study could be capable of maintaining a prolonged cerebral arterial contraction alone. Several other spasmogenic substances, including prostaglandins, norepinephrine, and hemoglobin, have been identified in CSF after SAH.31 These and other as yet unidentified substances circulating in CSF after aneurysm rupture may be responsible for vasospasm acting singly or synergistically with 5-HT. Thus, although our results do not indicate that 5-HT plays a major role in the pathogenesis of delayed vasospasm, 5-HT may still be of significance for the initiation of spasm. The relatively increased concentrations found in hemorrhagic CSF at operation suggest that 5-HT released from platelets shortly after the bleeding may be of importance in the early phase of vasospasm.

Acknowledgement

This study was supported by a grant from the Danish Medical Research Council.

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Epileptic Seizures in Cerebral Arterial Occlusive Disease

LEONARDO COCITO, M.D., EMILIO FAVALE, M.D., AND LIZIA RENI, M.D.

SUMMARY The occurrence of epileptic seizures was investigated in 141 patients with angiographically proven carotid or MCA occlusive disease. Epileptic seizures occurred some time during the clinical course of the disease in 17.3% of carotid patients and in 10.8% of MCA patients, being mainly represented by partial motor seizures. The pattern of occurrence of seizures in the natural history of cerebral arterial disease was different in the two groups. In the carotid group, epilepsy was the presenting symptom in 6.7% of patients, whereas no MCA patient had seizures prior to the appearance of a neurological deficit. Since epileptic seizures may complicate an otherwise asymptomatic carotid obstruction, angiography should be performed whenever the other standard investigations, including CT-scan, fail to reveal the cause of a late-onset epilepsy.

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EPILEPTIC SEIZURES are generally regarded as an uncommon symptom of cerebral ischemia. However, after the first observations of Moniz1,2 the occurrence of focal and generalized epileptic fits in carotid obstruction has often been emphasized in the literature. In a review of the early fifties Johnson and Walker4 reported an overall 20% incidence of epileptic seizures in carotid occlusive disease. Percentages varying from 10 to 30% are given by other authors.4-12 Even more relevant is the finding of Holmes18 that epilepsy was the first symptom of carotid occlusive disease in almost 10% of patients. Occasional reports of focal convulsions as the main feature of carotid stenosis can be found in the recent literature.14-18

The concept of a close association between epilepsy and carotid obstruction is far from being unanimously accepted, divergent opinions existing in both European and American literature. Some authors maintain that seizures seldom occur in patients with carotid artery disease and then mainly as a late sequel to a completed stroke,17-18 while others19 even question the relevance of seizures to the clinical pictures of carotid occlusive disease. Moreover, many recent reports on large groups of patients who underwent surgery for carotid obstruction did not record seizures in the preoperative picture, while other unusual presenting features of the disease, such as intellectual impairment and signs of brainstem dysfunction, received consideration.20-24

The growing attention focused on transient ischemic attacks (TIAs) seems to have fostered an increasing disregard of the relationship between epilepsy and cerebral ischemia, and the two diagnoses have even been considered as mutually exclusive.25

Seizures in obstructions of the middle cerebral artery (MCA) have not been regarded as an outstanding feature of the clinical picture, being included among second-order symptoms.5,8,10,12,20,27 The obvious inference is that epileptic attacks are more frequent in carotid than in MCA occlusive disease. Indeed, their actual incidence is difficult to assess on the basis of data so far available.5,10

Our aim has been to re-evaluate the occurrence of epileptic seizures in both carotid and MCA occlusive disease by investigating a group of patients with angiographically proven occlusions or stenosis of either artery. We wanted to verify whether epilepsy can really be regarded as an outstanding feature of carotid obstruction as pointed out by the classic literature; and, this being the case, to what extent it should be held peculiar to this syndrome rather than of MCA
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