Cerebral vasospasm: presence of mast cells in human cerebral arteries after aneurysm rupture

Preliminary note

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Mast cells contain heparin, histamine, hydrolytic enzymes, and possibly serotonin in metachromatic cytoplasmic granules, and are not visualized in routine histological preparations. Special fixation, frozen sections, and toluidine blue staining are essential for counting the number of mast cells in tissue sections. Histological preparations for counting mast cells were made from arteries of the circle of Willis in persons who died after chest or abdominal trauma (control group) and in patients who had subarachnoid hemorrhage (SAH) after aneurysm rupture. The arteries were removed within 6 hours of death, taking care to avoid damage to their structure, and were immersed in the fixative solution.

This preliminary note, reporting findings in only a few cases, is justified by the interesting discovery of a marked increase in mast cell population in the muscular layer of arteries after SAH. The series is small because of the difficulty in obtaining suitable material, since mast cells virtually disappear when autopsy is performed later than 6 hours after death. It is concluded from this study that there is an increase of mast cell population in cerebral arterial walls after SAH, mainly in the muscular layer, and that the number of mast cells is higher in arteries closer to the aneurysm.

**KEY WORDS** • subarachnoid hemorrhage • cerebral vasospasm • mast cell

The pathophysiology of cerebral vasospasm after subarachnoid hemorrhage (SAH) is not well established. Several substances have been cited as the cause of the reduction of the arterial diameter which is responsible for cerebral ischemia and for the increase in mortality and morbidity associated with rupture of an aneurysm. Serotonin has a potent effect on vasoconstriction of cerebral arteries, and some authors believe that this substance may be involved in the genesis of late vasospasm. Histamine, on the other hand, has a vasodilator effect, and might have a protective action on vascular physiology. Histamine has been quantitated on blood samples of patients who had SAH, and no significant difference with controls was found. Since mast cells are the main source of induced histamine in the human body and their granules might also contain serotonin, we decided to study the cerebral arteries of patients who died after SAH with a histological technique specifically for mast cells, correlating the results with signs of angiographic vasospasm.

**Materials and Methods**

Mast cells are difficult to demonstrate with common histological techniques; it is necessary to use early special fixation, frozen sectioning, and special staining. We used a fixative solution tested for human mast cells in a previous study: lead subacetate 1.0 gm, acetic acid 0.5 ml, and ethanol 50% in 100 ml solution.

The arteries of the circle of Willis were removed within 6 hours after death in 12 patients. Great care was taken to avoid damaging the arteries and to keep them away from water that can dissolve mast cell granules. After 24 hours of fixation, the arteries were cut transversely in frozen sections in pieces 50-μ thick using a cryostat. The sections were mounted on glass
slides and stained with toluidine blue 0.01% with a pH of 1.5 (buffer phosphate) for 3 minutes. The sections were washed with water, then dried and mounted with balsam. These preparations were then examined with the Zeiss photomicroscope (ocular ×16, objective ×40). The intima, media, and adventitia appear in blue, and the mast cells have characteristic purple metachromatic granules in their cytoplasm. Mast cells were counted in all microscopic fields, and the total number was divided by the number of fields examined.

**Results**

In six control adults (four males and two females) who died after chest or abdominal trauma without head injury, mast cells were almost completely absent from the cerebral arterial walls. The few that were found were all located in the adventitia (Fig. 1 left), in agreement with the findings of other authors.7,8,14,17

The arteries from six patients who died after SAH from aneurysm rupture were also examined. The number of mast cells found and the presence and degree of spasm seen angiographically are shown in Table 1. Four of these patients died before operation could be performed. They were in poor neurological condition and surgery was contraindicated. Specimens from these patients had a moderate number of mast cells located in the muscular layer. There was a minimal concentration in both patients who died 4 days after SAH (Cases 3 and 5: 0.1 mast cells per field), whereas the two patients who died on Days 14 and 18 (Cases 4 and 2) had more mast cells.

Two patients were operated on. One (Case 1) had a middle cerebral artery aneurysm, and angiography showed moderate vasospasm and a possible temporal hematoma. At operation we found severe edema; the aneurysm was clipped, and the patient deteriorated and died on the 3rd postoperative day with signs of cerebral ischemia. The other surgical patient (Case 6) was operated on in good clinical condition. He had a normal preoperative neurological examination and no vasospasm. Before the dura mater was opened, his carotid aneurysm ruptured, the brain became extremely edematous, and the aneurysm was not exposed. He died on the 2nd day after surgery. His

<table>
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<th>Case No.</th>
<th>Sex, Age (yrs)</th>
<th>Site of Aneurysm</th>
<th>Angiographic Spasm</th>
<th>Surgery</th>
<th>Death (days) Post-SAH</th>
<th>Postop</th>
<th>Mast Cells per Field</th>
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</table>

*MCA = middle cerebral artery, CA = carotid artery.
Mast cells in arteries after SAH

arteries showed a very high concentration of mast cells in the muscular layer (5.2 mast cells per field), most concentrated in the carotid artery from which the aneurysm arose (Fig. 1 right).

Discussion

Mast cells and their histological characteristics were first described 100 years ago by Paul Ehrlich before the Physiologic Society of Berlin, on January 17, 1879. Since then, more than 2000 papers have been published about this controversial cell. The simplest definition is that the mast cell is a connective tissue element which contains cytoplasmic granules that stain metachromatically under ordinary conditions. Mast cells produce heparin, histamine, and, at least in certain species, serotonin. The presence of serotonin in human mast cells is doubted by some authors. The mast cell is a pluripotent cell, a kind of emergency kit that contains a number of compounds that tissue may need, especially in regions exposed to local stress. Rosenblum verified that spasm could be evoked in pial arteries of rats by local instillation of Compound 48/80, which liberates mast cell vesicles. He also found that this spasm was not present in animals pretreated with reserpine, which decreases the amount of serotonin in mast cells.

Ibrahim, studying monkeys after proton irradiation, found an increase of perivascular mast cells in the nervous system. He believed that vasculopathy could be caused by serotonin released by mast cells that had been disrupted by radiation. However, most authors describe mast cells as having a protective activity in vascular physiology, with local liberation of histamine, heparin, and other substances that help repair areas of local injury.

We believe that it is difficult to reach definitive conclusions from our few cases, but we are very impressed by the high concentration of mast cells in Case 6; this patient had no vasospasm on angiography, and showed two to three times more mast cells in his cerebral arteries than the others who had vasospasm. Histochemical study of the substances present in these cells after SAH may add new information as to the treatment and prevention of cerebral vasospasm. If histamine is liberated by mast cells for protective vasodilation, the use of dexamethasone might be questioned in these patients, since histamine synthesis is blocked by this drug.

References


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