Surgical Experience With Cerebral Amyloid Angiopathy

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Cerebral amyloid angiopathy (CAA) is a well-recognized cause of spontaneous lobar intracerebral hemorrhage (ICH) in the elderly. Current estimates attribute 2–10% of all nontraumatic ICHs to CAA. The incidence of CAA-related changes within the brain increases with age.6,7 CAA may be responsible for a greater proportion of spontaneous ICHs among older patients. While understanding of the pathogenesis and associations of CAA have broadened, the treatment of patients with CAA-related ICH has remained controversial. Many authors recommend nonsurgical management of these patients because of concern regarding fragility of the vessel walls involved with CAA, difficulty in controlling intraoperative hemorrhage, and the possibility of recurrent postoperative hemorrhages.1,8,9 We report 11 patients with histologically confirmed CAA who underwent surgical procedures. No instances of abnormal intraoperative bleeding or recurrent hemorrhage were observed.

Subjects and Methods

We reviewed 11 patients with CAA who were evaluated and treated between May 1983 and January 1989. Nine patients presented with lobar ICH (four spontaneous and five traumatic) and the other two were diagnosed by brain biopsy during evaluations for dementia. Tissue specimens were obtained at the time of hematoma evacuation or brain biopsy. In the nine patients with ICH, biopsy specimens of the adjacent brain parenchyma were taken following hematoma removal. CAA was confirmed by vessel staining with Congo red and birefringence under polarized light. In addition, specimens were examined for the presence of neurofibrillary tangles and neuritic plaques.

Patient records were reviewed for pertinent medical history, including arterial hypertension, hypercholesterolemia, coronary artery disease, previous
cerebrovascular events, anticoagulant or antiplatelet drug use, and dementia. Hypertension was defined as blood pressure consistently elevated above 140/90 mm Hg, a history of elevated blood pressure treated with antihypertensive medications at the time of clinic visits and/or by telephone contact.

Follow-up evaluations were performed at return clinic visits and/or by telephone contact.

Results

All 11 patients (mean age 73 [range 62–82] years) had histologically verified CAA; nine were women (mean age 73 [range 62–82] years) and the other two were men (mean age 76 [ages 72 and 80] years). Presenting symptoms were spontaneous ICH, ICH in association with trauma, or dementia (Table 1).

Among the nine patients presenting with ICH, three had a history of arterial hypertension, six had an elevated serum cholesterol level, and three had coexistent coronary artery disease. Three patients had experienced previous cerebrovascular events (ischemic stroke in one and spontaneous ICH in two). One patient was receiving warfarin for recent deep-vein thrombosis and had an elevated prothrombin time (21 seconds, laboratory normal 10–13 seconds) on admission; no other patient had an abnormal prothrombin time, partial thromboplastin time, or platelet count. Aspirin was being taken regularly by one of the patients with a traumatic ICH. Two patients had a previously diagnosed dementia. Radiographic evaluations included computed tomography (CT) in all nine, cerebral angiography in seven, and magnetic resonance imaging (MRI) in four of the patients. CT demonstrated ICH in all nine. Angiography revealed an avascular mass in six (with associated vasospasm in one) and a sylvian arteriovenous fistula in one. MRI abnormalities included white matter changes, consisting of increased signal intensity on T2-weighted images, in two patients.

Four patients experienced a spontaneous ICH and the other five had an ICH following a minor fall. Two of the patients with a spontaneous ICH had suffered a previous spontaneous ICH (6 weeks and 8 months earlier, both managed nonsurgically) at a location separate from the presenting hemorrhage. The ICHs were unilobar in three patients and multilobar in the other six and involved the parietal lobe seven times, the frontal lobe four times, the temporal lobe four times, and the occipital lobe twice. One of the patients with a spontaneous ICH presented with bilateral lobar hematomas and during hospitalization developed a third spontaneous ICH in a different location.

No abnormal bleeding was encountered intraoperatively, and no patient experienced a recurrent hemorrhage during the remainder of the hospitalization or during follow-up (median 11 months, range 1 week to 74 months, n=7). Neurobehavioral testing was performed postoperatively in three patients, all of whom had deficits attributable to the location of the ICH, but without evidence of dementia. At dismissal six of the patients were improved neurologically and two were unchanged; the remaining patient had experienced a fatal cardiopulmonary arrest during the immediate postoperative period. Following discharge four of the patients continued to improve neurologically, two remained unchanged, one died 1 week after dismissal, and the other was lost to follow-up (Table 2).

In addition to the histologic features of CAA, seven of the nine patients were found to have neurofibrillary tangles and/or neuritic plaques in the

#### Table 1. Clinical Features of 11 Patients With Cerebral Amyloid Angiopathy Undergoing Operative Procedures

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Associated conditions</th>
<th>Previous diagnosis of dementia</th>
<th>Hematoma location (lobe)</th>
<th>Operative procedure</th>
<th>Neurologic outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>F</td>
<td>None</td>
<td>No</td>
<td>P</td>
<td>ICH evacuation</td>
<td>Improved*</td>
</tr>
<tr>
<td>77</td>
<td>F</td>
<td>None</td>
<td>Yes</td>
<td>F, P, T</td>
<td>ICH evacuation</td>
<td>Improved</td>
</tr>
<tr>
<td>62</td>
<td>F</td>
<td>Previous ICH</td>
<td>No</td>
<td>T</td>
<td>ICH evacuation</td>
<td>Improved*</td>
</tr>
<tr>
<td>71</td>
<td>F</td>
<td>Previous ICH</td>
<td>No</td>
<td>P, O</td>
<td>ICH evacuation</td>
<td>Unchanged</td>
</tr>
<tr>
<td>80</td>
<td>M</td>
<td>Fall, HTN</td>
<td>No</td>
<td>P, T</td>
<td>ICH evacuation</td>
<td>Died</td>
</tr>
<tr>
<td>82</td>
<td>F</td>
<td>Fall, aspirin</td>
<td>No</td>
<td>F</td>
<td>ICH evacuation</td>
<td>Improved*</td>
</tr>
<tr>
<td>72</td>
<td>F</td>
<td>Fall, HTN</td>
<td>No</td>
<td>F, P</td>
<td>ICH evacuation</td>
<td>Improved*</td>
</tr>
<tr>
<td>78</td>
<td>F</td>
<td>Fall, HTN, warfarin</td>
<td>No</td>
<td>P, T, O (s)</td>
<td>ICH evacuation</td>
<td>(P, T lobes only)</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>Fall</td>
<td>Yes (Alzheimer's disease)</td>
<td>F, P</td>
<td>ICH evacuation</td>
<td>Unchanged</td>
</tr>
<tr>
<td>80</td>
<td>F</td>
<td>None</td>
<td>Yes (NPH)</td>
<td>None</td>
<td>Brain biopsy, VP shunt</td>
<td>Improved</td>
</tr>
<tr>
<td>72</td>
<td>F</td>
<td>HTN</td>
<td>Yes</td>
<td>None</td>
<td>Brain biopsy</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

F, female; M, male; ICH, intracerebral hemorrhage; HTN, hypertension; NPH, normal-pressure hydrocephalus; P, parietal; F, frontal; T, temporal; O, occipital; s, separate hematoma; VP, ventriculoperitoneal.

*Continued to improve neurologically after dismissal.
TABLE 2. Neurologic Status of Nine Patients Undergoing Evacuation of CAA-Related Hematomas

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Preoperative status</th>
<th>Postoperative status</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>F</td>
<td>Arousal to noxious stimulation, localization with L arm, R hemiplegia</td>
<td>Speech fluent with few repetition errors, R hemiparesis, ambulates with cane</td>
<td>Lives independently. Last seen in clinic 39 months after surgery</td>
</tr>
<tr>
<td>77</td>
<td>F</td>
<td>R decorticate posturing, L hemiparesis</td>
<td>Alert, mouthing words, purposeful with R arm, L hemiparesis</td>
<td>Died in nursing home 1 week after dismissal</td>
</tr>
<tr>
<td>62</td>
<td>F</td>
<td>Lethargic, L hemiparesis</td>
<td>Normal motor exam</td>
<td>Lives independently. Last seen in clinic 11 months after surgery</td>
</tr>
<tr>
<td>71</td>
<td>F</td>
<td>Mild L hemiparesis</td>
<td>Unchanged</td>
<td>Lives in nursing home, needs assistance with ADLs. Last telephone contact 74 months after surgery</td>
</tr>
<tr>
<td>80</td>
<td>M</td>
<td>L hemiparesis</td>
<td>Unchanged</td>
<td>Fatal cardiopulmonary arrest 4 days after surgery</td>
</tr>
<tr>
<td>82</td>
<td>F</td>
<td>L hemiparesis</td>
<td>Improved L hemiparesis</td>
<td>Lives in nursing home. Last telephone contact 17 months after surgery</td>
</tr>
<tr>
<td>72</td>
<td>F</td>
<td>L hemiparesis</td>
<td>Improved L hemiparesis</td>
<td>Lives independently. Last seen in clinic 5 months after surgery</td>
</tr>
<tr>
<td>78</td>
<td>F</td>
<td>L hemiparesis</td>
<td>Normal motor exam</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>Lethargic, R hemiparesis</td>
<td>Unchanged</td>
<td>Died in nursing home 3 months after dismissal</td>
</tr>
</tbody>
</table>

CAA, cerebral amyloid angiopathy; F, female; M, male; L, left; R, right; ADLs, activities of daily living.

surgical specimens; these tangles and/or plaques were in sufficient numbers to be consistent with Alzheimer’s disease in this age group by suggested criteria.10 In the other two patients there was insufficient viable brain tissue to examine for meaningful numbers of neuritic plaques or tangles. Only two of the nine patients had the premorbid clinical diagnosis of a degenerative dementia.

One patient also had an arteriovenous malformation that was congophilic focally but separate from the other vessels within the brain parenchyma that were amyloid-positive. Two of these nine patients were also used as controls for A4 peptide staining performed in a previously published series of brain vascular malformations.11 In both of these controls congophilic vessels were A4-positive, and in one several vessels negative with Congo red were positive with A4.

Among the two patients presenting with dementia, the diagnosis of CAA without ICH was made in both from brain biopsy specimens obtained during dementia evaluations. One patient presented with a 4-year history of dementia, increasing gait difficulty, and urinary disturbance and was found to have hydrocephalus by CT; MRI also revealed white matter disease. A diagnosis of normal-pressure hydrocephalus was made, and a brain biopsy was performed at the time of ventriculoperitoneal shunt placement. Postoperatively, the patient’s ambulation was improved. The second patient had the recent onset of dementia and evidence of bilateral prefrontal dysfunction on neurobehavioral testing. MRI revealed extensive bilateral abnormalities involving both the gray and the white matter. Brain biopsy specimens from both patients demonstrated CAA with neurofibrillary tangles and neuritic plaques in sufficient numbers to diagnose Alzheimer’s disease. No hemorrhages occurred following these surgical procedures.

Discussion

Small and medium-sized leptomeningeal and cortical vessels are predominantly affected by CAA, in which twisted beta-pleated sheet fibrils are deposited in the vessel wall, resulting in the characteristic staining with Congo red and birefringence under polarized light.12 Segmental fibrinoid degeneration in some of the vessels affected by amyloid has also been shown.13 Hemorrhage as the presenting feature of CAA has been attributed to suspected brittleness and fragility of the involved vessels.5,8,14 The widespread nature of these features is also believed to account for the occurrence of both multiple and recurrent hemorrhages, as was seen in one and three of the 11 patients in this series, respectively. Both multiple8,15,16 and recurrent17-21 CAA-related hemorrhages have been reported, and recurrent hemorrhages are now thought to occur in approximately 10% of cases.22 Because of concern regarding difficult-to-control intraoperative bleeding and postoperative hemorrhages, previous authors have recommended nonsurgical therapy for patients with CAA-related hemorrhages.1,8,9,23 Two patients in this series and other patients with recurrent CAA-related hemorrhages19,21 have been managed nonsurgically and showed neurologic improvement. Other authors have recommended biopsy of the adjacent brain if hematoma evacuation is deemed necessary.21 In this
series nine patients underwent surgical evacuation of an ICH and biopsy of the adjacent brain parenchyma, with no instances of abnormal bleeding or recurrent hemorrhage. This finding suggests that patients with ICH in whom CAA is suspected may safely undergo ICH removal.

Two of the nine patients with CAA-related ICH experienced fatal cardiopulmonary arrests postoperatively, one several days after ICH evacuation and the other 1 week following dismissal from the hospital, for a surgical mortality rate of 22%. This mortality rate is lower than that observed by Cosgrove et al, who reported 75% mortality (three of four) in patients undergoing evacuation of CAA-related hematoma. Their overall mortality rate of 94% (15 of 16) is consistent with the 90% mortality rate reported by other authors, whose patients also received either aggressive medical or surgical treatment.

Patients have also developed ICH following ventricular shunt placement, again attributed to pathologic changes in the vessel wall. One patient in this series underwent brain biopsy and ventriculoperitoneal shunt placement, and another underwent brain biopsy alone, without evidence of abnormal bleeding or postoperative complications.

Six of the nine patients undergoing ICH removal had improved neurologically by the time of dismissal from the hospital, whereas two remained unchanged (Table 2). During follow-up four of the improved patients continued to improve and now live independently or are able to perform their activities of daily living in a care facility. These results indicate that not only may patients safely undergo ICH evacuation, but neurologic improvement may often be seen during both the immediate postoperative period and continued follow-up. The observations of neurologic improvement and lower mortality in this series compared with those reported previously may reflect the severe neurologic impairment of the other patients at the time of presentation.

Predisposing factors for ICH were reviewed in these patients to identify possible causal relations to CAA. Hypertension was present in three of the nine patients, consistent with the incidence of hypertension in patients of this age and in other series of patients with CAA. Other authors have not considered it important in the causation of CAA, although hypertension may contribute to the occurrence, size, or extent of hemorrhages in patients with CAA. The coagulation status may also have contributed to the ultimate size of the hematoma in the one patient who was treated with warfarin and developed an ICH after a fall. The incidence of hypercholesterolemia (six of nine) and coexistent coronary artery disease (three of nine) appears appropriate for this age group, and autopsy studies have found no correlation between the severity of CAA and that of cerebral or visceral atherosclerosis. One patient in this series had a history of ischemic stroke, an association that has been reported previously.

Most (seven) of the nine patients with ICH in this series were women, a finding that has been reported by others but not substantiated from compiled series of patients. Also, autopsy studies have not shown a sex predilection for CAA. Thus, except for a documented history of head trauma in five of the nine patients, no other factors were clearly identified as causally related to the development of ICH in these patients with CAA.

A discrepancy has been noted between the anatomic distribution of the changes of CAA and the sites of hemorrhage. The most severe CAA has been found in the temporal, parietal, and occipital lobes, whereas CAA-related hemorrhages have been reported most often in the frontal and parietal regions. In this series most (six) of the nine patients presented with multilobar hemorrhages, which were most commonly located in the parietal and less frequently in the frontal, temporal, and occipital lobes (three, three, and two, respectively). The unilobar hemorrhages (three of nine patients) were evenly distributed among the parietal, frontal, and temporal lobes. These findings are consistent with those reported previously, in which ICH infrequently involves the occipital lobe.

In addition to ICH as a presenting feature of CAA, a history of dementia has also been considered significant. Clinically evident dementia is seen in approximately 30–40% of patients with CAA and was found in four (36%) of the 11 patients in this series, although only two (22%) of the nine patients presenting with ICH had a history of dementia. A disparity exists, however, between the relatively low clinical incidence of dementia and the presence of the pathologic features of Alzheimer’s disease reported in the tissue specimens from patients with CAA. Neurofibrillary tangles and/or neuritic plaques were identified in nine of the 11 patients in this series, although only four of the 11 were clinically demented. The high incidence of neurofibrillary tangles and neuritic plaques with CAA has been reported previously, but no obvious relation has been established between the severity and extent of CAA and that of neurofibrillary tangles and plaques, nor between the presence and severity of these histopathologic changes and dementia.

References

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KEY WORDS • amyloid • cerebral hemorrhage • surgery
Surgical experience with cerebral amyloid angiopathy.
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*Stroke*. 1990;21:1545-1549
doi: 10.1161/01.STR.21.11.1545

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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