Surgical Risk of Hemorrhage in Cerebral Amyloid Angiopathy

Zelko Matkovic, MB, BS; Stephen Davis, MD, FRACP; Michael Gonzales, MB, BS, FRCPA; Renate Kalnins, MB, BS, BMedSci, FRCPA; and Colin L. Masters, MD

Cerebral amyloid angiopathy (CAA) is characterized pathologically by deposition of amyloid in the walls of small and medium-sized arteries, arterioles, and, less often, capillaries and veins of the leptomeninges and cerebral cortex. 1-3 CAA usually occurs in the absence of systemic amyloidosis. The condition is increasingly recognized as a common cause of sporadic nontraumatic lobar intracerebral hemorrhage (ICH) in normotensive elderly subjects. 4-6 According to autopsy studies, approximately 5-10% of all cases of primary ICH are due to CAA. 1,7,8 The majority of cases are sporadic, but familial forms of CAA occur, particularly in the Netherlands. 9

Several routine autopsy studies suggest that cerebrovascular amyloid deposition increases with age, 10 occurring in approximately 30% of patients over the age of 60 years 10-12 and in some 90% of patients with Alzheimer's disease. 13,14 One third of patients with CAA have clinically apparent dementia, and a similar number are hypertensive. 1,7,15 Recurrent and multiple ICH are a feature of CAA. 4,16

The treatment of ICH and, in particular, the role of neurosurgical evacuation of supratentorial hematomas remain controversial. 17,18 Patients with lobar supratentorial hemorrhage who initially have relative preservation of their conscious state and who develop a progressive neurological deficit may be candidates for neurosurgical intervention. 18 Torack, 19 in an oft-cited report, detailed the case of a 71-year-old man with normal pressure hydrocephalus and clinically asymptomatic CAA who developed a massive and fatal ICH after brain biopsy and ventriculoperitoneal shunt insertion. This 19 and subsequent 18,20-22 case reports of uncontrollable perioperative hemorrhage and recurrent postoperative bleeding have led some authors to suggest that neurosurgical intervention in patients with CAA is hazardous. To determine the risk of hemorrhage precipitated by neurosurgery in patients with CAA, we retrospectively reviewed 16 patients in whom the diagnosis had been pathologically confirmed. In this group of patients, 15 neurosurgical procedures were performed.

Subjects and Methods

We identified 16 sporadic cases of histologically proven CAA by a retrospective review of the medical records.
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FIGURE 1. Computed tomogram on admission of patient 2 demonstrating right temporal lobe hemorrhage with intraventricular extension.

records of six Melbourne teaching hospitals between 1984 and 1990. The diagnosis was made at autopsy in eight patients and from neurosurgical biopsy specimens in the remaining eight. Four patients in the latter group also subsequently came to autopsy.

Clinical features were derived from an analysis of the patient's medical record, including a review of the patient's age and sex, details of the presenting illness, and the presence or absence of hypertension, dementia, or prior stroke. Review of the examination findings included mental state and the presence or absence of neurologic deficits. We also analyzed the results of radiological investigations (Figure 1), medical or surgical intervention, and eventual outcome. In the neurosurgical group, we paid particular attention to any evidence of intraoperative or postoperative hemorrhage and the postoperative clinical course. Postoperative cerebral computed tomography (CT scanning) was not performed unless there was a clinical suspicion of cerebral hemorrhage.

While the aim of this study was to ascertain the risk of neurosurgically precipitated hemorrhage in patients with CAA, we also analyzed the clinical features of the eight nonoperated patients identified over the same period. As these patients were all diagnosed at autopsy, we did not regard the two groups as being comparable.

Tissues obtained at craniotomy for clot evacuation in eight patients were fixed in 10% neutral buffered formalin for 2 weeks, and survey blocks were taken from the frontal, parietal, temporal, and occipital lobes bilaterally (Figure 2). All tissues were embedded in paraffin and stained with hematoxylin and eosin, phosphotungstic acid hematoxylin, and Congo red, and the sections were examined by light and polarized microscopy. Sections from two biopsies and three autopsies were also examined by peroxidase-anti-peroxidase immunohistochemistry with an antiserum against the βA4 amyloid protein (Figure 3). This protein is the major component of amyloid, which accumulates in vessel walls in CAA and in neuritic plaques and vessel walls in Alzheimer's disease.23

Results

In the 16 cases studied, there were nine men and seven women aged 49-86 (mean 73) years. Five patients had a history of hypertension. Only two patients had a history of dementia, although detailed neuropsychological examination had not been performed in any patient. Six patients had a history of stroke, three with cerebral infarction, two with ICH, and one with subarachnoid hemorrhage.

Fifteen neurosurgical procedures were performed in eight patients (Table 1). In this group, six patients presented with lobar cerebral hemorrhage, one had a cerebellar hemorrhage, and one had the recent onset of partial seizures with radiological signs of a temporal lobe mass lesion. This was excised, and CAA was diagnosed on pathological examination. The clinical features of the other seven patients were typical of cerebral hemorrhage. Impaired conscious state and focal neurologic deficits were frequent, each occurring in five patients; headache and vomiting were also prominent, each occurring in four patients. All operated patients had cerebral CT scanning, and three had cerebral digital subtraction angiography.

The initial neurosurgical procedures consisted of clot evacuation in six patients, ventriculoperitoneal shunt insertion in one patient (performed for hydrocephalus complicating ICH), and mass lesion excision in one. Subsequent neurosurgical procedures were performed in three of the eight patients. One patient required reexploration 2 months after clot evacuation because of a persisting contrast-enhancing nodule at the site of the initial surgery detected on CT scanning. Another patient was treated by ventriculoperitoneal shunt insertion 16 days postoperatively after the development of symptomatic hydrocephalus. The third patient had repeated clot evacuation from the site of the initial surgery 2 days later. Six months after clot evacuation, this patient developed a symptomatic cerebral abscess. Despite drainage procedures on three separate occasions, the abscess reaccumulated, finally necessitating a lobectomy.

Recurrent hemorrhage may have been precipitated by neurosurgery in one patient (patient 1, Table 1). Two days after the initial evacuation of an occipital hematoma, this patient deteriorated with evidence of recurrent hemorrhage at the operative site on CT scan.
FIGURE 2. Photograph of coronal section through cerebral hemispheres of patient 2 showing old right temporal hemorrhage. Second, recent left frontoparietal lobar hemorrhage is present. There is intraventricular spread.

He underwent urgent repeat clot evacuation. In the other three patients, recurrent lobar cerebral hemorrhages occurred at a site different from that of the initial surgery 9 days (patient 2, Table 1), 6 weeks (patient 6, Table 1), and 10 months (patient 5, Table 1) after the initial surgery; two patients died. In all the patients identified, there was no reported difficulty in obtaining hemostasis at surgery.

Three of the surgically treated patients were alive 4 years, 3 years, and 4 months after surgery. Two of these patients have returned to work, and the third has been confined to a nursing home. Three patients died of recurrent ICH (two lobar and one putaminal hypertensive hemorrhage), and two patients died of pneumonia. These deaths occurred between 13 days and 3 years after the initial hospitalization.

Eight conservatively treated patients with CAA were identified (Table 2). All presented with lobar ICH. Clinical features were typical of ICH, with headache, vomiting, and focal neurological signs occurring in two, three, and four patients respectively; all patients had a variable degree of impaired consciousness. All eight patients died during the first few days after hospitalization, and a diagnosis of CAA was made at autopsy. Five deaths were attributed to brain stem compression, two were caused by pulmonary embolism, and one was due to recurrent hemorrhage.

In this nonsurgical group, recurrent lobar ICH was seen in two patients. One patient (patient 11, Table 2) had a fatal parietal hemorrhage 33 days after initially being hospitalized with a frontal lobar hematoma. In another patient (patient 10, Table 2), three lobar hemorrhages at separate locations were documented over 3 years prior to the terminal stroke.

Discussion

Formation of neuritic plaques, degeneration of neurofibrils, and accumulation of amyloid in the walls of vessels are characteristic changes in the brains of aged subjects, but these changes are most severe in persons with Alzheimer's disease. The major component of cerebrovascular and plaque core amyloid is a 4-kDa protein (βA4), which is derived by proteolytic cleavage from a larger precursor protein (APP) that has the structural features of an integral transmembrane protein. Accumulation of βA4 protein in the extracellular space and in the adventitia and outer media of cerebral vessels is thought to result from abnormal processing of APP. Two familial forms of CAA (Dutch and Icelandic) have been described. In the Dutch form a mutated βA4 protein accumulates in vessel walls, whereas the major component of vascular amyloid in the Icelandic form is a protease inhibitor, cystatin-C, also known as γ-trace protein.

The mechanism of cerebral hemorrhage in CAA is poorly understood. Postulated causes include rupture of the amyloid-impregnated vessels due to their heightened fragility, rupture of vessels as a result of segmental fibrinoid degeneration, and microaneurysm formation. While patients with lobar ICH may be candidates for neurosurgical evacuation, concerns about the risks of precipitated hemorrhage in
FIGURE 3. Histologic appearances of cerebral amyloid angiography in material obtained at surgery in patient 8. Amyloid, highlighted by immunoperoxidase staining with β44 antibody, is seen in adventitia and outer media of small cortical arteries and arterioles (arrows). (β-A4 antiserum 1:200, hematoxylin counterstain, ×95.)

patients with CAA have been based on isolated reports of relatively simple neurosurgical procedures precipitating massive or fatal intracranial bleeding. Various reports have indicated that efforts to evacuate a blood clot may be complicated by difficulties in establishing hemostasis, with diffuse oozing from the wall of the hematoma and unexpected intraoperative and postoperative hemorrhage. In addition, it has been suggested from autopsy reviews of CAA and ICH, in which no cases were found to have died of cerebral herniation and brain stem compression, that clot evacuation may be unnecessary. Only two other communications have reported the results of neurosurgical intervention in a series of patients with CAA and ICH. Greene et al described no instances of abnormal perioperative bleeding or recurrent hemorrhage in nine patients with CAA who underwent evacuation of intracerebral hematomas. Keeffauver et al reported four long-term survivors after surgery for ICH in five patients with CAA.

The clinical features of our 16 patients conform to previous descriptions of CAA, with lobar ICH being the characteristic finding. The cerebral mass lesion (patient 4, Table 1), a rare manifestation of CAA, has been previously described. Briceno et al reported a patient with a history of recent seizures and a frontal mass lesion on CT scan whose biopsy showed CAA, with a few of the amyloid-laden vessels cuffed by mononuclear cells and an occasional multinucleated giant cell and marked reactive gliosis. The histological features were similar to those documented in our patient.

While the eight nonoperated patients cannot be regarded as controls for those who underwent neurosurgery, the former exemplify the characteristic features of CAA, namely, recurrent and multiple lobar hemorrhage. Furthermore, in contrast to other reports, brain stem compression resulting from lobar hemorrhage was a common cause of death in this group.

In three of the four patients with recurrent, postoperative ICH the ictus was a delayed event, occurring at least 1 week and up to 10 months after the surgical procedure and distant from the initial evacuation site. In this series, neurosurgical intervention could be deemed to have precipitated further clinically significant bleeding in only one patient. Clearly, in this retrospective study, recurrent minor postoperative hemorrhages that were not of clinical significance were not detected.
TABLE 1. Presenting Features, Management, and Outcome of Surgical Group

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Diagnosis</th>
<th>Surgery</th>
<th>Recurrent hemorrhage</th>
<th>Cause</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/68/M</td>
<td>R occipital hemorrhage</td>
<td>1 day</td>
<td>2 days, clot evacuation; 6 months, abscess drainage and lobectomy</td>
<td>2 days, R occipital</td>
<td>10 months</td>
</tr>
<tr>
<td>2/80/M</td>
<td>R temporal hemorrhage</td>
<td>4 days</td>
<td>None</td>
<td>Recurrent hemorrhage</td>
<td>13 days</td>
</tr>
<tr>
<td>3/59/M</td>
<td>R parietal hemorrhage</td>
<td>7 days</td>
<td>None</td>
<td>None</td>
<td>...</td>
</tr>
<tr>
<td>4/49/F</td>
<td>L temporal mass lesion</td>
<td>41 days</td>
<td>None</td>
<td>None</td>
<td>...</td>
</tr>
<tr>
<td>5/61/F</td>
<td>L parietal hemorrhage</td>
<td>6 days</td>
<td>None</td>
<td>10 months, R parietal; 3 years, putaminal hemorrhage</td>
<td>3 years</td>
</tr>
<tr>
<td>6/74/M</td>
<td>R temporoparietal hemorrhage</td>
<td>2 days</td>
<td>None</td>
<td>42 days, L parietal</td>
<td>42 days</td>
</tr>
<tr>
<td>7/69/M</td>
<td>Cerebellar hemorrhage</td>
<td>1 day</td>
<td>16 days, shunting</td>
<td>None</td>
<td>41 days</td>
</tr>
<tr>
<td>8/82/F</td>
<td>L parietal hemorrhage</td>
<td>1 day</td>
<td>None</td>
<td>None</td>
<td>...</td>
</tr>
</tbody>
</table>

M, male; F, female; R, right; L, left.

No conclusion can be drawn from this small study regarding the efficacy of neurosurgical evacuation of intracerebral hematomas in patients with CAA. Moreover, these patients are at high risk of recurrent hemorrhage. Nonetheless, we suggest that neurosurgical procedures, particularly hematoma evacuation, are not contraindicated in patients with suspected CAA. A possible diagnosis of CAA should not preclude a patient from being considered for neurosurgical clot evacuation if he fulfills other clinical criteria.

Acknowledgments

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TABLE 2. Presenting Features and Outcome of Nonsurgical Group

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Diagnosis</th>
<th>Recurrent hemorrhage</th>
<th>Cause</th>
<th>Time from most recent hemorrhage (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/80/F</td>
<td>R parietal hemorrhage</td>
<td>None</td>
<td>Brain stem compression</td>
<td>1</td>
</tr>
<tr>
<td>10/69/F</td>
<td>L frontal hemorrhage</td>
<td>3 lobar before terminal hemorrhage over 3 years</td>
<td>Brain stem compression</td>
<td>1</td>
</tr>
<tr>
<td>11/79/M</td>
<td>Bifrontal hemorrhage</td>
<td>R parietal</td>
<td>Recurrent hemorrhage</td>
<td>33</td>
</tr>
<tr>
<td>12/78/M</td>
<td>L frontoparietal hemorrhage</td>
<td>None</td>
<td>Brain stem compression</td>
<td>1</td>
</tr>
<tr>
<td>13/81/M</td>
<td>L parietooccipital hemorrhage</td>
<td>None</td>
<td>Brain stem compression</td>
<td>4</td>
</tr>
<tr>
<td>14/82/F</td>
<td>R parietooccipital and L parietal hemorrhages</td>
<td>None</td>
<td>Pulmonary embolism</td>
<td>18</td>
</tr>
<tr>
<td>15/86/F</td>
<td>L frontoparietal hemorrhage</td>
<td>None</td>
<td>Brain stem compression</td>
<td>3</td>
</tr>
<tr>
<td>16/78/M</td>
<td>R frontoparietal hemorrhage</td>
<td>None</td>
<td>Pulmonary embolism</td>
<td>9</td>
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</tbody>
</table>

F, female; M, male; R, right; L, left.
References


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