Postoperative Outcome of 37 Patients With Lobar Intracerebral Hemorrhage Related to Cerebral Amyloid Angiopathy

Akifumi Izumihara, MD; Tokuhiro Ishihara, MD; Naoki Iwamoto, MD; Katsuhiro Yamashita, MD; Haruhide Ito, MD

Background and Purpose—Several recent studies have suggested that neurosurgical procedures are not contraindicated in patients with cerebral amyloid angiopathy (CAA). The purpose of this study was to elucidate the clinical factors influencing the outcome of patients with CAA-related intracerebral hemorrhage (ICH) treated surgically.

Methods—A total of 50 neurosurgical procedures (42 intracerebral hematoma evacuations, 4 ventriculoperitoneal shunts, 3 ventricular drainages, and 1 brain biopsy) were performed in 37 patients with CAA-related ICH. To ascertain the clinical factors that may influence their postoperative outcome, their clinical data (demographics, medical history, recurrent lobar hemorrhage, radiographic characteristics, multiple lobar hemorrhage, surgical details, and postoperative hemorrhage) were examined retrospectively and subjected to multivariate analysis.

Results—Twenty patients (54%) had a good outcome, and only 4 (11%) died. Parietal hematomas, advanced age (>75 years), and intraventricular hemorrhages had significant adverse influence on the postoperative outcome. Clinically significant postoperative hemorrhage requiring evacuation occurred after 2 (5%) of 42 intracerebral hematoma evacuations. Postoperative hemorrhage did not have significant adverse influence on the outcome.

Conclusions—Neurosurgery can be performed relatively safely in patients with CAA-related ICH, and their postoperative outcome is better than that reported previously. Surgical treatment should be considered for such patients aged >75 years without a parietal hematoma and intraventricular hemorrhage. (Stroke. 1999;30:29-33.)

Key Words: amyloid ■ intracerebral hemorrhage ■ outcome

In cerebral amyloid angiopathy (CAA), amyloid β-protein is deposited in the media and adventitia of cortical and leptomeningeal blood vessels and is associated with loss of vascular smooth muscle cells in the media. This may interrupt the first phase of hemostasis, vasoconstriction, which may make establishing hemostasis during neurosurgery difficult in patients with CAA. Previous studies have indicated that neurosurgical procedures in patients with CAA may cause uncontrollable perioperative and postoperative hemorrhage (POH) and neurological deterioration. Consequently, several authors have recommended treating CAA-related intracerebral hemorrhage (ICH) nonsurgically.

On the other hand, several recent studies have suggested that neurosurgical procedures in patients with CAA do not precipitate clinically significant POH and that intracerebral hematoma evacuation improves their neurological condition. Over the last decade, we have operated on 37 patients with CAA-related lobar ICH. In this study, we examined the demographics, medical history, radiographic characteristics, and surgical details of these patients retrospectively and subjected them to multivariate analysis to elucidate the clinical factors that may influence the postoperative outcome.

Subjects and Methods

Over a 10-year period (1987 to 1996), 37 patients with CAA-related lobar ICH underwent neurosurgery at our institute and 6 associated hospitals. From their medical records, we determined each patient’s sex and age; the presence of dementia, hypertension, and/or any systemic bleeding tendency; the use of antihypertensive, anticoagulant, and/or antiplatelet agents; and the history of previous lobar ICH. All 37 patients underwent preoperative, postoperative, and subsequent CT scans. The locations, sizes, and shapes of the hematomas were evaluated by preoperative CT scan. If multiple lobar hemorrhage, which was defined as ≥2 separate hemorrhages in multiple lobes, had occurred, the largest hematoma was examined. The location of each hematoma was defined as the lobe in which it was mainly located; its size was graded as small (<30 mL), medium (≥30 mL and <60 mL), or large (≥60 mL); and its shape was described as lobular, irregular, or round. The presence of intraven-
tricular hemorrhage (IVH) was also noted. POH, which was defined as any new additional ICH confirmed by postoperative CT scan within 48 hours of neurosurgery, was evaluated as small (<30 mL), medium (≥30 mL and <60 mL), or large (≥60 mL). Progressive ventriculal dilatation was monitored by subsequent CT scan. To detect any vascular anomalies preoperatively, 22 patients underwent cerebral angiography and 2 underwent MRI.

A total of 50 neurosurgical procedures (42 intracerebral hematoma evacuations, 4 ventriculoperitoneal shunts, 3 ventricular drainages, and 1 brain biopsy) were performed. The surgical details examined comprised the surgical techniques used to evacuate the hematoma and the interval between hemorrhage and hematoma evacuation. We also established whether there was subarachnoid hemorrhage or subdural hematoma by intraoperative observation. POH evacuations were excluded from this study.

With respect to recurrent lobar hemorrhage, we examined the frequency of previous lobar ICHs and whether there was histological evidence of CAA previously. In cases of CAA-related recurrent lobar hemorrhage, we examined the radiographic characteristics and surgical details of the latest CAA-related lobar ICH. In contrast, whether POH had occurred was examined after all 50 neurosurgical procedures.

The patients were followed up for 3 days to 93 months (mean, 32.5 months) postoperatively. The postoperative outcome except death was assessed at least 1 month after the latest CAA-related ICH treated surgically with the use of the best estimate of the Glasgow Outcome Scale (good recovery, moderately disabled, severely disabled, and vegetative survival).

For statistical analysis, the postoperative outcome was categorized into 2 groups: good (good recovery or moderately disabled) or poor (severely disabled, vegetative survival, or death). Univariate analysis involved the use of the χ² test or Fisher’s exact test to identify the clinical factors associated with the postoperative outcome. The multiple logistic regression model was used to assess which risk factors predict the postoperative outcome. Independent variables with a univariable probability value of <0.05 were selected for inclusion in the multivariable model and were tested by the backward procedure. A probability value of <0.05 was considered significant.

CAA was diagnosed by the presence of yellow-green birefrin- gence on exposure to polarized light after tissue staining with Congo red in surgical specimens of the adjacent brain parenchyma obtained during intracerebral hematoma evacuation or cortical biopsy. The surgical specimens were also subjected to immunohistochemical staining with the use of a monoclonal antibody raised against a synthetic peptide consisting of residues 8 to 17 of amyloid β-protein. Finally, the sections were incubated with diaminobenzenidine and were counterstained with hematoxylin.

**Results**

**Clinical Background**

The 37 patients with CAA-related lobar ICH comprised 16 men and 21 women (Table 1). Their ages ranged from 61 to 91 years, with a mean age of 75.6 years. Seven patients (19%) had previously been diagnosed as having dementia. Fifteen patients (41%) had a history of hypertension, and 9 (60%) of these 15 patients were taking antihypertensive agents. Their blood pressure was controlled well. No patient had a systemic bleeding tendency or was taking anticoagulant or antiplatelet agents. Eleven patients (30%) suffered recurrent lobar hemorrhage, which occurred at the same location as the previous lobar ICH in 4 (36%) of these 11 patients. Eight (73%) of these 11 patients were aged ≥75 years, and 8 (73%) had a history of hypertension. Eight of these 11 patients had had 1 previous lobar ICH, and 3 had had 2 previous lobar ICHs. Of a total of 14 previous lobar ICHs, 5 had been treated surgically and diagnosed histologically as CAA related.

Five CAA-related ICHs (14%) presented as multiple lobar hemorrhage (2 separate intracerebral hematomas simultaneously in multiple lobes). Eleven intracerebral hematomas were mainly located in the parietal lobe, 9 in the frontal lobe, 11 in the occipital lobe, and 6 in the temporal lobe. Eleven intracerebral hematomas were small, 13 medium, and 13 large. Twenty-three intracerebral hematomas were lobular, 8 irregular, and 6 round. Five CAA-related ICHs (14%) perfo- rated the ventricular wall. Thirteen patients (35%) had pro- gressive ventricular dilatation, and all 13 patients with pro- gressive ventricular dilatation had had subarachnoid hemorrhage or IVH. Cerebral angiogram and MRI did not demonstrate any vascular anomalies.

We performed 27, 7, and 3 intracerebral hematoma evacuations by means of craniotomy, trephination or small crani- otomy, and burr hole, respectively. Intracerebral hematoma evacuation and drainage through a single burr hole was performed with the use of a CT-guided stereotactic technique. Seven intracerebral hematomas were evacuated on the day of the hemorrhage (day 0), 18 on days 1 to 3, and 12 on day 4 or later (mean interval, 2.7 days). During intracerebral hema- toma evacuation, we observed subarachnoid hemorrhage 31 times (84%) and subdural hematoma 9 times (24%). POH occurred after 4 intracerebral hematoma evacuations (2 small and 2 medium-sized POHs) but after no other neurological procedure. Both small POHs were <10 mL and asymptomatic. In contrast, both medium-sized POHs were symptomatic and required evacuation. Consequently, clinically significant POH requiring evacuation occurred after 2 (5%) of 42 intracerebral hematoma evacuations. No large or fatal POH occurred.

**Multivariate Analysis**

The postoperative outcome was good (good recovery/moderately disabled) for 20 (14/6) patients (54%) and poor (severely disabled/vegetative survival/death) for 17 (7/6/4) (46%) (Table 1). Only 4 patients (11%) died. Of the 16 independent variables subjected to univariate analysis, 15 were selected for inclusion in the multivariable model. Multiple logistic regression analysis demonstrated that parietal hematomas (odds ratio, 10.0; P=0.01), advanced age (≥75 years) (odds ratio, 35.0; P=0.02), and IVHs (odds ratio, 50.5; P=0.03) had significant adverse influence on the postoperative outcome (Table 2). Surgical factors, including POH, did not have significant influence on the outcome. One patient with POH had a good outcome (moderately disabled), and 3 had a poor outcome (severely disabled or vegetative survival). Both severely disabled patients with small POH were aged ≥75 years and had a parietal hematoma, and 1 vegetative survival patient with medium-sized POH had 2 previous CAA-related lobar ICHs treated surgically. The medium-sized POH oc- curred after the first intracerebral hematoma evacuation, and the patient did not have any neurological deficits after the POH evacuation.

**Histological Findings**

The amyloid-laden vessels of all 37 patients (42 lobar ICHs) reacted with the anti–β-protein antibody, and 25 patients (68%) had senile plaques that were anti–β-protein antibody...
reactive (Figure). Senile plaques were seen in 5 (71%) of 7 patients who had previously been diagnosed as having dementia.

Discussion
CAA is well recognized as a common cause of spontaneous lobar ICH in elderly normotensive individuals. In many cases of CAA-related lobar ICH, the hematomas involve both the cortex and the white matter, extend from the cortex to the subarachnoid space, and are lobular in shape.11 Furthermore, multiple and recurrent ICHs are a feature of CAA-related ICH.12–15 However, it is impossible to establish the diagnosis of CAA after radiographic examination of patients with lobar ICH at present. Histological examination of brain tissue obtained during surgery is still necessary for the diagnosis of CAA.

According to a review of 35 patients who underwent neurosurgery for CAA-related ICH reported by Leblanc et al,11 13 (37%) died after intracerebral hematoma evacuation, and only 7 (20%) were neurologically well (good recovery or moderately disabled) postoperatively. However, many of these patients were in a poor neurological condition preoperatively because of severe intracranial hypertension caused by the mass effect of the hematoma, and we consider this to be

### TABLE 1. Clinical Factors Influencing Postoperative Outcome of Patients With CAA-Related ICH

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>Outcome (Glasgow Outcome Scale)</th>
<th>P*</th>
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</thead>
<tbody>
<tr>
<td>Total (n=37)</td>
<td>14/6 (54%)</td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n=16)</td>
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</tr>
<tr>
<td>Women (n=21)</td>
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<td>Age, y</td>
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<tr>
<td>&lt;75 (n=16)</td>
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</tr>
<tr>
<td>≥75 (n=21)</td>
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<tr>
<td>Dementia</td>
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<tr>
<td>Yes (n=7)</td>
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<td>Hypertension</td>
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<tr>
<td>Yes (n=15)</td>
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<tr>
<td>RLH</td>
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<td>Yes (2) (n=3)</td>
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<td>MLH†</td>
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<tr>
<td>ICH location†</td>
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<td>Temporal (n=6)</td>
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<td>Occipital (n=11)</td>
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<tr>
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<tr>
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<td>ICH size†</td>
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<tr>
<td>Small (n=11)</td>
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<td>ICH shape†</td>
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<td>Irregular (n=8)</td>
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<td>Lobular (n=23)</td>
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<td>IVH†</td>
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<td>SAH‡</td>
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<td>2/2 (44)</td>
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<tr>
<td>Surgical technique‡</td>
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<td>Craniotomy (n=27)</td>
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<tr>
<td>Trephination (n=7)</td>
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<tr>
<td>Burr hole (n=3)</td>
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**TABLE 1. Continued**

<table>
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<tr>
<th>Interval‡</th>
<th>Outcome (Glasgow Outcome Scale)</th>
<th>P*</th>
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<tr>
<td>Day 4 (n=12)</td>
<td>4/3 (58)</td>
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<tr>
<td>Days 1–3 (n=18)</td>
<td>9/3 (67)</td>
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<tr>
<td>Day 0 (n=7)</td>
<td>1/0 (14)</td>
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<tr>
<td>POHS§</td>
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<tr>
<td>No (n=33)</td>
<td>14/5 (58)</td>
<td></td>
</tr>
<tr>
<td>Yes (n=4)</td>
<td>0/1 (25)</td>
<td></td>
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</table>

GR indicates good recovery; MD, moderately disabled; SD, severely disabled; VS, vegetative survival; D, death; RLH, recurrent lobar hemorrhage; MLH, multiple lobar hemorrhage; PVD, progressive ventricular dilatation; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; Interval, interval between hemorrhage and evacuation; Yes (1), 1 previous lobar ICH; and Yes (2), 2 previous lobar ICHs. Values are prevalences (%).

*χ² test or Fisher’s exact test.
†The largest hematoma was examined in cases of MLH, and the latest CAA-related lobar ICH was examined in cases of RLH.
‡The latest intracerebral hematoma evacuation was examined in cases of RLH.
§Whether POH had occurred was examined after all 50 neurosurgical procedures.

### TABLE 2. Multiple Logistic Regression Analysis of Risk Factors for an Adverse Postoperative Outcome of Patients With CAA-Related ICH

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal hematoma</td>
<td>10.0</td>
<td>2.0–50.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Advanced age (≥75 y)</td>
<td>35.0</td>
<td>2.3–527.4</td>
<td>0.02</td>
</tr>
<tr>
<td>IVH</td>
<td>50.5</td>
<td>1.6–1585.0</td>
<td>0.03</td>
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</table>

OR indicates odds ratio.
the main reason for their poor outcome. In our series of patients with hematomas of various sizes (10 to 130 mL), 20 (54%) had a good outcome (good recovery or moderately disabled), and only 4 (11%) died. The postoperative outcome in the present study was better than that reported previously.

An advanced age (≥75 years) was a significant risk factor for an adverse postoperative outcome. Most of the patients who became vegetative or died were aged ≥75 years, whereas three quarters of the patients younger than this had a good outcome. Therefore, we consider the age of patients with CAA-related ICH to be an important factor in determining whether surgical treatment is indicated. The incidence of CAA increases with advancing age, which suggests that the older the patient, the higher the risk of CAA-related ICH and recurrent lobar hemorrhage. Recently, Passero et al reported that patients with recurrent ICH without aneurysms, arteriovenous malformations, brain tumors, or hemorrhagic disorders were often older than those without recurrent ICH and that ICH recurrence was associated with a high mortality rate (70%). Similarly, in our study of CAA-related ICH, patients with recurrent lobar hemorrhage tended to be older than those without recurrent lobar hemorrhage. Although only 1 (9%) of our 11 patients with recurrent lobar hemorrhage died, 8 (73%) had a poor outcome. Moreover, univariate analysis demonstrated that recurrent lobar hemorrhage was associated with an adverse postoperative outcome (P = 0.04). Accordingly, prevention of recurrent lobar hemorrhage is important to avoid poor outcome in patients with CAA-related ICH, but it is impossible at present. We believe that the elderly (≥75 years), who have a high risk of recurrent lobar hemorrhage, should be treated nonsurgically.

The radiographic factors with significant influence on the postoperative outcome were ICH location and IVH. A parietal hematoma was a significant risk factor for an adverse postoperative outcome. Most of the parietal hematomas extended to the frontal lobe and involved the pyramidal tract of neurons in our series. These findings indicate that intracerebral hematoma evacuation does not improve severe motor deficit associated with a frontoparietal hematoma. On the other hand, it has been reported previously that a temporal hematoma is often fatal. In our series, however, 5 (83%) of 6 patients with a temporal hematoma had a good outcome (good recovery), which is partly explained by the greater percentage of patients with a small hematoma. IVH also had significant adverse influence on the postoperative outcome in our study. Similarly, previous studies have indicated that patients with secondary IVH, which is defined as intraventricular rupture from intraparenchymal hemorrhage, has an adverse outcome. We believe that intraventricular rupture from CAA-related lobar ICH, which tends to extend to the surface of the brain, damages brain parenchyma more extensively.

The problem of hemorrhage induced by neurosurgery in patients with CAA has been emphasized in several previous studies. Certainly, bleeding occurs easily during neurosurgery, and it is often difficult to achieve hemostasis in patients with CAA. However, the pathogenesis of such bleeding is poorly understood at present. Several recent studies have demonstrated that amyloid β-protein damages vascular smooth muscle cells and/or vascular endothelial cells, suggesting that CAA inhibits vascular contraction and/or platelet adhesion. In our series, we observed intraoperative oozing of blood from some hematoma walls, and this could be controlled by the use of an absorbable hemostat (oxidized cellulose or gelatin sponge) or fibrin glue.

Consequently, clinically significant POH requiring evacuation occurred after only 2 (5%) of 42 intracerebral hematoma evacuations. Recently, Palmer et al reported that the incidence of POHs requiring evacuation after 129 evacuations of intracerebral hematomas due to various causes was 3.1%. These findings indicate that neurosurgery induces POH in patients with CAA less frequently than previously thought. Contrary to previous isolated reports, we observed no POH after 11 neurosurgical procedures performed through a single burr hole (4 ventriculoperitoneal shunts, 4 hematoma drainages, and 3 ventricular drainages). Furthermore, no large POH occurred, and none of the 4 patients who developed POH died in our series.

In conclusion, neurosurgery can be performed relatively safely in patients with CAA-related ICH, and their postoperative outcome is better than that reported previously. Risk factors for an adverse postoperative outcome are parietal hematomas, advanced age, and IVHs. Surgical factors, including POH, do not have significant influence on the outcome. Surgical treatment should be considered for such patients aged <75 years without a parietal hematoma and IVH.

References


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