Lobar intracerebral hemorrhage

A clinical, radiographic, and pathological study of 29 consecutive operated cases with negative angiography

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The authors operated consecutively on 50 patients with lobar intracerebral hemorrhage during a prospectively designed study period from January, 1986, to March, 1990. They investigated the correlations between the underlying causes and the clinicoradiographic features in 29 patients who showed no angiographic vascular abnormalities, in order to elucidate the operative indication for such cases. Patients with ruptured saccular aneurysm or trauma were not included in this study. There were 15 males and 14 females, ranging in age from 7 to 76 years (mean 52.4 years). Histological diagnoses of the surgical specimens were as follows: vascular malformation in nine cases (arteriovenous malformation (AVM) in six and cavernous malformation in three), microaneurysm in 11, cerebral amyloid angiopathy in six, and brain tumor in two; in the remaining case the cause was not verified histologically. The underlying cause was determined in 96.5% of cases. The mean patient age was lowest in the cavernous malformation group (27.0 years), followed by the AVM (45.8 years), microaneurysm (59.8 years), and cerebral amyloid angiopathy (70.0 years) groups. Four patients with vascular malformation (three AVM's and one cavernous malformation) had previous episodes of bleeding at the same site, whereas none of those with microaneurysms or cerebral amyloid angiopathy had such episodes. On computerized tomography (CT) scans, the round to oval hematoma was related to the presence of an AVM or cavernous malformation in contrast to microaneurysms and cerebral amyloid angiopathy. Upon infusion of contrast material, variable enhancement was seen in five (two AVM's and three cavernous malformations) of the nine vascular malformations while no enhancement was noted in any patient with microaneurysm or cerebral amyloid angiopathy at the acute stage. Subarachnoid extension of the hematoma was associated with cerebral amyloid angiopathy significantly more frequently than with AVM’s (p < 0.05) and microaneurysms (p < 0.01).

The results suggest that clinicoradiographic pictures in cases with negative angiography are quite different among the three major pathological categories; namely, vascular malformation (AVM and cavernous malformation), microaneurysm, and cerebral amyloid angiopathy. It is suggested that the underlying etiology of a given lobar intracerebral hemorrhage with negative angiography may be predicted by a combination of patient age, history of previous bleeding at the same site, hematoma shape, and subarachnoid extension of the hematoma on CT scans. Based upon these findings, the authors discuss operative indications for such cases.

Key Words · lobar intracerebral hemorrhage · vascular malformation · microaneurysm · amyloid angiopathy · angiography · computerized tomography

Lobar intracerebral hemorrhage (ICH) is known to have a variety of causes, including vascular malformations, microaneurysms (so-called "hypertensive"), cerebral amyloid angiopathy, and brain tumors.12-14,16,20,23,41,44-46 Although the operative indication in such cases has long been controversial4,17,32,44 no doubts have been raised about surgically treating patients with lobar ICH secondary to angiographically apparent vascular malformations and with life-threatening large hematomas. However, the therapeutic options in cases with small or medium-sized hematomas and with negative angiography are still subject to discussion, mainly because no definitive clinicoradiographic features have been identified that indicate its underlying causes. Ropper and Davis40 concluded from their experience with 26 patients that lobar ICH should not routinely be treated by surgery. On the other hand, Crowell et al.4,25 stressed the potential benefits of surgical evacuation of large, accessible lobar hematomas. The high incidence of angiographically occult vascular malformations in patients with lobar ICH and negative angiograms40,44 may warrant surgical
evacuation of this type of hematoma regardless of hematoma size or the presence of hypertension, except in elderly patients with suspected amyloid angiopathy complicated by dementia.  

As we have reported previously, damage to the surrounding brain can be minimized with the aid of an operating microscope, and thus the morbidity rate can be quite low. In that earlier series, 11 (73%) of the 15 lobar ICH patients had a good outcome. Furthermore, angiographically occult vascular malformations and other underlying causes were found in 12 (80%) of the patients with normal angiograms. Because the number of patients was too small and the study was retrospective, we designed a prospective study to obtain the incidence of angiographically occult vascular malformations and other lesions causing lobar ICH, and to elucidate the operative indications for this particular type of hematoma by investigating the correlations between the underlying pathologies and the clinicoradiographic features.

**Clinical Material and Methods**

**Patient Population**

From January, 1986, to March 1990, 72 patients with lobar ICH (excluding cases caused by the rupture of a saccular aneurysm or trauma) were admitted to our department, either directly or as a referral. Surgery was carried out when the patient met one or more of the following criteria: 1) an angiographically apparent arteriovenous malformation (AVM) or other vascular abnormalities; 2) disturbance of consciousness (somnolence to coma) on admission; 3) neurological deterioration after admission; 4) a previous history of bleeding at the same site; and 5) written consent obtained from patients (if they were alert and <70 years of age) and their relatives, based on the possibility of an angiographically occult vascular malformation as a cause of bleeding if the hematoma was not in eloquent sites. As a result, 50 of the 72 patients were assigned to undergo surgery. Of the 50 patients, 42 met one or more of the first four criteria while only eight met the fifth criterion. One patient with multiple cavernous malformations developed recurrent hemorrhage at the same site during the study period. Accordingly, 51 operations were performed.

Forty-two patients underwent angiography before surgery; the remaining eight did not, mostly because emergency surgery was required for a life-threatening hematoma. The patient with multiple cavernous malformations did not undergo angiographic studies at the time of recurrent bleeding. Angiography revealed an AVM in 12 patients, early venous filling in one, and no vascular abnormalities in 29. These 29 patients are the subject of the present study. All but four patients were operated on by one of the authors (S.W.). Surgery was carried out on Days 0 to 3 after the hemorrhage in 11 patients, on Days 4 to 7 in seven, on Days 8 to 14 in four, and on Day 15 or thereafter in seven. All clinical records and radiographic data were reviewed and analyzed in terms of patient age, sex, the presence of hypertension and of previous bleeding, recurrence of bleeding after surgery, neurological symptoms and signs, computerized (CT) tomography features, location of hematomas, and outcome.

**Pathological Examination**

In all patients, the hematoma and its wall were thoroughly investigated under an operating microscope using the technique described elsewhere. Resected solid tissues or abnormal vascular nodules covered with blood clot and having vascular connections with the surrounding brain were examined histologically. The removed specimens were cut into two pieces after fixation in 10% formalin for 24 to 48 hours. Three or four ordinary sections about 2.5 μ thick were made starting from the cut surface of one of the two paraffin-embedded blocks and were stained with hematoxylin and eosin, Congo red, elastica van Gieson, and Azan-Mallory methods. When no pathological diagnosis was reached from this routine examination, the entire specimen was sectioned serially at a thickness of 2.5 μ and all other sections were examined using the same staining methods. In cases with cerebral amyloid angiopathy, immunohistochemical staining for beta-protein and cys-
Outcome

Two Arteriovenous malformations (AVMs) were identified in three patients with lobar intracerebral hemorrhage (ICH) and negative angiography. Etiological breakdown includes vascular malformation (diagonal lines), microaneurysm (dots), cerebral amyloid angiopathy (cross-hatching), brain tumor (BT), and unknown (UNK).

Clinicopathological correlation was performed using monoclonal antibodies for these two amyloid proteins.

Results

Causes and clinical features in the 29 patients with ICH and negative angiography are given in Table 1 and the age distribution is shown in Fig. 1. Vascular malformations were verified in nine cases (AVM’s in six and cavernous malformations in three), microaneurysms in 11, cerebral amyloid angiopathy in six, and brain tumor in two (one glioblastoma and one metastatic adenocarcinoma); the pathological diagnosis was not definitive in the remaining case. Thus, in this series the underlying causes were identified in 96.5% of cases.

Arteriovenous Malformations

The six patients with AVM’s ranged in age from 8 to 65 years (mean ± standard deviation 45.8 ± 20.9 years). Two were male and four female. In three patients, the AVM had bled previously at the same site as the current bleeding (Table 1). One patient had suffered hemorrhage at the same site prior to this study period. The histological diagnosis at that time was cavernous malformation (Fig. 2A and C), but pathological examination by serial sectioning at this admission revealed an AVM (Fig. 2B and D). The level of consciousness on admission was characterized as alert in two cases, somnolent in three, and comatose in one. On CT scans, the hematoma was lobulated in one patient and round to oval in the other five. Nodular enhancement was seen in two patients. The hematoma extended to the subarachnoid space in two of the six patients (Table 2). Outcome at a follow-up period of 6 months to 5 years after surgery was good (normal life with or without minor neurological deficit) in all six patients.

Cavernous Malformations

The age of the three patients with cavernous malformations ranged from 7 to 62 years (mean 27.0 ± 30.4
years). Two were male and one female. One patient with multiple cavernous malformations had a history of bleeding at the same site and suffered hemorrhage at another site after surgery (Table 1). The level of consciousness on admission was characterized as alert in all three patients. On CT, the hematoma was round to oval in all patients, with variable contrast enhancement (Fig. 3). The hematoma extended to the subarachnoid space in only one patient (Table 2). Outcome was good in two patients and fair (moderate neurological deficit) in one.

Microaneurysms

The age of the 11 patients with microaneurysm ranged from 44 to 73 years (mean 59.8 ± 12.0 years). There were five men and six women. Six patients had a history of hypertension. In no patient was there a previous bleeding episode at the same site (Table 1). The level of consciousness on admission was characterized as alert in five patients, somnolent in four, and stuporous in two. On CT, the hematoma was lobulated in eight patients and round to oval in three (Fig. 3). No enhancement was noted in any patient at the acute stage. Subarachnoid extension of the hematoma was seen in only one patient (Table 2). Outcome was good in 10 patients and fair in one.

Microaneurysms fell into two categories as described by Fisher:7 miliary aneurysm and bleeding globe (ruptured artery). Because a microaneurysm may only be recognized pathologically as a bleeding globe (ruptured artery) if it has ruptured, these two categories were combined and listed as microaneurysms.41 Among the 11 microaneurysms studied, a parent artery was not verified histologically within the removed tissues of two.41 Nine patients had verified parent arteries; one microaneurysm was found in five patients, two microaneurysms in two, three microaneurysms in one, and four microaneurysms in one. In these cases, the parent artery supplying each microaneurysm was identified under the operating microscope as well as histologically (Fig. 4). The size of the parent arteries ranged from 25 to 230 µ in luminal diameter near the orifice to the microaneurysm. The walls and parent arteries of the microaneurysms were negative on Congo red staining in all 11 cases.

Cerebral Amyloid Angiopathy

In the six patients with cerebral amyloid angiopathy, ages ranged from 65 to 76 years (mean 70.0 ± 3.8 years). There were four men and two women. Only two patients had a history of hypertension. None had experienced previous bleeding at the same site, although one patient had suffered a lobar ICH at another site 3 years before. Lobar ICH occurred at another site after surgery in two patients (Table 1). The level of consciousness on admission was characterized as alert in one case, somnolent in three, and stuporous in two. On CT, the hematoma was lobulated and extended to the subarachnoid space in all six patients. The lobulation appeared more prominent in patients with cerebral amyloid angiopathy than in patients with an AVM or microaneurysm. No enhancement was noted in any patient at the acute stage (Table 2 and Fig. 3). Outcome was good in three cases and fair in two; one patient died of recurrent hemorrhage at another site.

In all six patients with cerebral amyloid angiopathy, both beta-protein and cystatin C were present within the wall of the small arteries in the subarachnoid hematoma as well as in the subpial brain parenchyma surrounding the hematoma (Fig. 5). The arterial wall stained intensely with Congo red and showed birefringence on polarized light. In one patient, a microaneurysm was found in the hematoma wall (Fig. 5).

Statistical Analysis

A statistically significant difference among the above four groups was observed in the following factors as shown in Tables 1 and 2: 1) mean age; 2) previous bleeding at the same site; 3) shape of the hematoma;

| TABLE 2 |
| Computerized tomography (CT) features in 29 surgically treated cases of lobar intracerebral hemorrhage (ICH) with negative angiography |

<table>
<thead>
<tr>
<th>Cause of Lobar ICH</th>
<th>Noncontrast CT</th>
<th>Postcontrast CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shape of Hematoma</td>
<td>Subarachnoid Extension</td>
</tr>
<tr>
<td>arteriovenous malformation (AVM)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>cavernous malformation</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>microaneurysm</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
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<td>0</td>
</tr>
<tr>
<td>brain tumor</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>unknown</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>totals</td>
<td>16</td>
<td>13</td>
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* Statistical significance: between the AVM group and the microaneurysm group, and between the cavernous malformation group and the cerebral amyloid angiopathy group, p < 0.05; between the AVM group and the cerebral amyloid angiopathy group, p < 0.01 by Fisher's exact test.

† Statistical significance: between the AVM group and the cerebral amyloid angiopathy group, p < 0.05; between the microaneurysm group and the cerebral amyloid angiopathy group, p < 0.01 by Fisher's exact test.
Lobar intracerebral hemorrhage

Fig. 3. Computerized tomography scans showing the shape and extension of the intracerebral hematoma typical for three underlying causes. Left: Scan from a 62-year-old man with cavernous angioma. An oval hematoma is seen in the left frontal lobe. Center: Scan from a 72-year-old woman with a microaneurysm (shown in Fig. 4). A lobulated subcortical hematoma is noted in the right temporal lobe. Right: Scan from a 72-year-old woman with cerebral amyloid angiopathy. Photomicrographs of the surgical specimen from this patient are shown in Fig. 5. A multilobulated hematoma is seen in the left frontoparietal region extending to the subarachnoid space (arrows). The lobulation of the hematoma appears quite prominent compared to that of the case shown in the scan at center.

and 4) subarachnoid extension of the hematoma with secondary subarachnoid hemorrhage.

Discussion

The results of the present study suggest that at least three major underlying etiologies of a given lobar ICH with negative angiography may be identified based on a combination of age, history of previous bleeding in the same site, shape of the hematoma, and presence of subarachnoid extension of the hematoma on CT. These etiologies include vascular malformations (AVM's and cavernous malformations), microaneurysm, and cerebral amyloid angiopathy. We were unable to differentiate AVM's from cavernous malformations based upon the CT features alone. The hematoma had a tendency to involve the temporal lobe more frequently than other lobes in patients with microaneurysm and cerebral amyloid angiopathy; however, no significant difference was

Fig. 4. Photomicrographs of the surgical specimen removed from a 72-year-old woman with hypertension. A = artery; H = hematoma. Left: A small artery (arrow) is connected to a microaneurysm (MiAN), the wall of which has ruptured at two sites (arrowheads) where the collagenous layer has been lost. The diameter of the microaneurysm is 1700 μ and of its parent artery is 140 μ. Elastica van Gieson, × 17.5. Right: Higher magnification of the portion indicated by the arrow, left. The internal elastic lamina has lost its corrugation and appears degenerated at the orifice to the microaneurysm. Elastica van Gieson, × 87.5.
ferentiation may emerge with repeat MR studies. Furthermore, because the signal intensity varies with the age of the hematoma, one may be unable to identify the underlying pathology. In this regard, a small iso- or slightly hyperdense nodular or tubular defect devoid of hematoma in its periphery on CT scans ("nidus sparing sign") may be of help in some cases to distinguish angiographically occult vascular malformation from the surrounding hematoma (Fig. 2). In patients with disturbance of consciousness due to a large hematoma, faster neurological evaluation is mandatory prior to emergency surgery. In such situations, CT is currently superior to MR imaging in terms of shorter scan time and more accurate delineation of the location and extent of an acute hematoma. Rapid progress in MR technology, however, could solve such problems in the future.

**Vascular Malformations**

Recurrent bleeding from vascular malformations, particularly from cavernous malformations, is said to be quite high and incomplete removal of the lesion may result in further bleeding, as occurred in one of our patients (Fig. 2). Hence, in lobar ICH patients with round to oval hematoma at an accessible location visualized on CT and with a history of previous hemorrhage (particularly younger patients), surgery is strongly recommended regardless of hematoma size in order to prevent recurrent hemorrhage.

In this series, the vascular malformation was found in 30% of the patients with lobar ICH and negative angiography. This discovery rate is quite high compared with that of other lobar ICH series reported in the CT era. This may be related to our careful microsurgical search of the hematoma and its wall for abnormal vascular nodules, and our meticulous histological investigation of the surgical specimens using the serial sectioning technique if necessary.

**Microaneurysm**

Microaneurysm as a cause of lobar ICH has previously been found only in autopsy specimens. In many series of lobar ICH, the cases in which no bleeding source was discovered were diagnosed as hypertensive or unknown in origin. Hinton, et al., meticulously examined the surgical specimens taken from their patients with lobar ICH and cerebellar hemorrhage but in no case was a Charcot-Bouchard microaneurysm identified. The cause of the hemorrhage was found only in 33.3% of their surgically treated cases. The bleeding source, including microaneurysms, was identified in 96.5% of our series. This rate is again quite high compared to that of other series.

The multiple microaneurysms in four of our patients may have ruptured simultaneously or in an avalanche fashion resulting in enlargement of the hematoma, as discussed by other authors. The number of microaneurysms, however, seemed unrelated to hematoma size. Rather, the size of the parent arteries appeared to

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**FIG. 5.** Photomicrographs of the hematoma (He) capsule (A) and arteries in the cortex overlying the hematoma (B and C) removed from a 72-year-old woman 14 days after hemorrhage. A: A microaneurysm (MiAN) about 500 μ in diameter is seen in the center of the figure. The wall of the parent artery is strongly positive for Congo red stain, but the wall at its orifice to the microaneurysm (arrows) has lost its ability to stain. Congo red, × 50. B and C: Photomicrographs of specimen that have been incubated for monoclonal antibodies against beta-protein (B) and cystatin C (C). The arterial wall contains dense reaction products to both. Peroxidase-antiperoxidase method for amyloid proteins, × 160.
Lobar intracerebral hemorrhage

be associated with that of the hematoma although there was no statistically significant relationship.

It may be questioned whether the microaneurysms found in the surgical specimens were the actual cause of the hemorrhage. There was contiguity of the masses of red blood cells and the surrounding hematoma in all cases. Furthermore, only solid tissues covered by blood clot with an arterial connection in the surrounding brain were found at surgery at the periphery of the hematoma. In two cases with possible microaneurysm the parent artery was not revealed histologically, although it was seen under the microscope during surgery. Accordingly, it is reasonable to conclude that these microaneurysms were the cause of the bleeding.

Five (45%) of the 11 patients with microaneurysms had no hypertension previously or at admission. In contrast, nine patients with putaminal hemorrhage and four patients with cerebellar hemorrhage, who were operated on during the same period and whose microaneurysm was verified histologically, had a history of hypertension, and blood pressure was high at admission. Lipton, et al., observed a significantly lower occurrence of hypertension in patients with lobar ICH than in those with thalamic and basal ganglionic hemorrhage. Some pathologists have speculated on the different pathophysiological mechanisms involved in the vascular wall between lobar perforating arteries and lenticulostriate arteries, based on the histological findings seen in autopsy specimens. A comparative histological study on the vascular changes in microaneurysms and their parent arteries in both groups of patients is under way.

Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy has been widely known as a main cause of lobar ICH in the elderly, whether or not related to hypertension. Microaneurysm rupture is also ascribed to hematoma formation in cases with cerebral amyloid angiopathy as in cases of so-called "hypertensive lobar ICH." Deposition of amyloid proteins in the vascular wall of the small subarachnoid and cortical arteries with secondary hyalin or fibrinoid degeneration of their walls may weaken the arterial wall, resulting in microaneurysm formation followed by rupture of the microaneurysm or of the already crippled artery itself.

Due to the fragile wall of the ruptured artery and of other arteries surrounding the hematoma, hemostasis after evacuation of the hematoma may be quite bothersome. Postoperative hematoma formation in the same site has been reported, although there was no such occurrence in our series. Therefore, evacuation surgery is not recommended as long as the patient's neurological condition allows conservative treatment. Of the 22 patients in this series who were not treated surgically, cerebral amyloid angiopathy was assumed as the cause of hemorrhage in two, based upon CT scans as described above. So far, only 18 patients with cerebral amyloid angiopathy in whom evacuation surgery was carried out, including ours, have been reported.

In addition to multiple hematomas in elderly patients, measurement of the cerebrospinal fluid (CSF) cystatin C content may be of help in differentiating cerebral amyloid angiopathy from other causes. The cystatin C concentration in the CSF is lower in patients with hereditary and nonhereditary cerebral amyloid angiopathy than in patients with other cerebrovascular diseases. Of the six patients in the current series, the CSF cystatin C was measured in two, and both showed low titers, 60 and 56 ng/ml, respectively. Shimode, et al., reported that a concentration of less than 100 ng/ml was likely to be related to the presence of nonhereditary cerebral amyloid angiopathy. The CSF cystatin C titer should thus be measured in patients suspected of having cerebral amyloid angiopathy unless the intracranial pressure is too high for CSF withdrawal. Even after surgery, measurement of CSF cystatin C levels reinforces the etiological diagnosis.

The overall outcome was good in 24 (83%) of the 29 cases. The low morbidity rate in this prospective study series could also be ascribed to the minimal damage to the surrounding brain due to utilizing microsurgery. Good outcomes, however, were obtained in only 50% of the cerebral amyloid angiopathy cases, which is probably related to the advanced patient age and to the presence of recurrent hemorrhage at other sites.

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References


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