Lobar Cerebral Hemorrhage from Amyloid Angiopathy: Clinical, Neuroimaging, Pathologic and Outcome Correlations

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Abstract- Cerebral amyloid angiopathy (CAA) contributes to sporadic lobar intracerebral hemorrhage in older patients, especially those who are more than 70 years old. In clinical practice, a diagnosis of CAA refers to the Boston Criteria, which requires that "definitive" cases be confirmed by pathologic evidence at autopsy. A "Probable" case, means that there is clinical support and that pathologic evidence is available by biopsy from the craniotomy for patients with severe lobar intracerebral hemorrhage. Cerebral amyloid that is deposited in cortical vessels is revealed by apple-green birefringence under polarized light using Congo-red stain. Rebleeding after a first primary intracerebral hemorrhage is common. This paper describes five cases of aged patients with lobar cerebral hemorrhage and craniotomy with hematoma evacuation and biopsy. Pathological results all showed amyloid angiopathy. Various outcomes are discussed, and the literature is reviewed. Findings show that although patients with CAA were at high risk of recurrent hemorrhage after surgery, the mortality rate was relatively low despite the severity of lobar intracerebral hemorrhage.

Key Words: Cerebral amyloid angiopathy, Lobar intracerebral hemorrhage, Outcomes

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INTRODUCTION

Sporadic lobar intracerebral hemorrhage (LICH) has been well recognized in the past, and cerebral amyloid angiopathy (CAA) is one of the contributory factors in aged patients. A previous study revealed that about half of the non-traumatic cases of LICH in patients more than 70 years old were due to CAA[(1)]. In clinical practice, the diagnosis of CAA refers to the Boston Criteria, wherein cases are considered "confirmed" and "definite" by pathologic evidence at postmortem autopsy. However, because of the low autopsy rate in Taiwan, a definitive case of CAA is difficult to prove. However, "probable" cases, which means supporting clinical evidence and pathologic presentation, are available when patients with severe LICH submit to craniotomy and tissue biopsy and amyloid deposition is shown in the cortical vessels.

The major clinical features of CAA include dementia and LICH, but not every patient shows the coexistence of the two features. Initial brain CT may differentiate hemorrhagic from ischemic stroke when a patient

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presents with focal neurological signs. In hemorrhagic stroke, the sites of hematoma may distinguish the precipitating factors: basal ganglion related hemorrhage from hypertension, and lobar hemorrhage from CAA or tumor bleeding[1]. To obtain confirmation of CAA, it is necessary to arrange for tissue biopsy in advance, but not all patients are willing to undergo this procedure. However, the risk for CAA increases if a patient suffered from recurrent lobar hemorrhage. In other words, the value of pathological proof appreciates, because it significantly influences the outcomes for a patient and the therapeutic choices for variable situations in the future. The purpose of this article is to discuss the clinical presentations, neuroimaging findings and pathological results of patients with LICH from CAA, and to do an analysis of the outcomes after surgical treatments.

MATERIALS AND METHODS

Using the registrations of patients with LICH from January 1997 to December 2002 in our department, there were five patients with pathologic evidence of CAA. Of the five identified patients, there were four males and one female with ages ranging from 65 to 83 years old. The precipitating factors included diabetes mellitus, hypertension and dementia. The associated manifestations included headache, hemiparesis or hemiplegia, disturbances in consciousness, and seizure. The determination of initial consciousness level used the Glasgow Coma Scale (GCS) recorded on the chart in the emergency room. The volume of hemorrhage[2] was calculated from half the product of the greatest transverse diameter, perpendicular diameter and the thickness of the lesion estimated in the CT slices. The surgical intervention pointed to the patient having a hematoma evacuation via craniotomy accompanied with or without a shunting procedure. Tissue biopsy for each patient was done using Hematoxylin-eosin stain, polarized light and Congo-red stain. The outcomes were analyzed by (1) the frequency of recurrent hemorrhage (RH), (2) recurrent operative hemorrhage (ROH), which was defined as any new additional ICH confirmed by post-operative CT scan within 48 hours of neurosurgery, and (3) the Rankin scale (a measurement of functional neurological deficits).

RESULTS

Regarding the findings in Table 1, the mean age of our patients was 76.2 years. Only Patient 3 had a history of hypertension, and Patient 5 diabetes mellitus. There was no one with dementia judging by the chart records or the family statements. Our patients had not used anti-

Table 1. *Baseline and clinical of patients*

Patient	1	2	3	4	5
Age(y/o)	83	77	73	83	65
Sex	male	male	male	male	female
Hypertension	-	-	+	-	-
Diabetes mellitus	-	-	-	-	+
Anticoagulant use	-	-	-	-	-
Dementia	-	-	-	-	-
Headache	-	+	+	-	-
Hemiparesis	-	-	+	+	+
Seizure	-	-	-	-	+
GCS score	7	9	9	10	12

GCS: Glasgow Coma Scale.

Table 2. *The initial brain CT characteristics of patients*

Patient	1	2	3	4	5
CT					
Hematoma site	Left P-O	Right frontal	Left F-P	Right P-O	Right F-P
Hematoma volume(ml)	24.5	31.5	30.0	31.7	24.8
IVH	+	+	+	+	-

P-O: parieto-occipital; F-P: fronto-parietal; IVH: intraventricular hemorrhage.

Table 3. *The surgery therapy and outcomes of patients*

Patient	1	2	3	4	5
Surgery					
Evacuation	+	+	+	+	+
Shunt	+	-	+	-	-
Rankin scale (discharge)	3	2	5	4	3
ROH	-	-	-	-	-
RH	+	-	+	-	+
Frequency	1	-	3	-	1
Hematoma site					
First	Left occipital		Left frontal		Right F-P
Second	-		Left T-P		-
Third	-		Right F-P		-
Mean interval(day)	5		299		261

ROH: recurrent operative hemorrhage; RH: recurrent hemorrhage; F-P: fronto-parietal; T-P: temporo-parietal.

coagulant drugs. In clinical manifestations, there were two patients with headache, and three with hemiparesis or hemiplegia. Patient 5 had a seizure as the initial presentation of LICH. All of the five patients showed a disturbance in consciousness, and the mean GCS score was 9.4. The CT findings shown in Table 2 reveal three patients with hematoma located on the right side, and two on the left side. The hemorrhage distributed in various lobes including frontal, parietal and occipital with intraventricular (IVH) in four patients. The mean volume of hematoma was 28.5ml. For early diagnosis by neuroimaging, all of the five patients had brain CT (Fig. 1), and on the occurrence of RH, only Patient 5 underwent brain MRI (Fig. 2). The others had a repeat brain CT. Table 3 shows that all of the five patients received craniotomy with hematoma evacuation, and two patients underwent shunting drainage as follows: Patient 1 was catheterized with an external ventricular drainage, and Patient 3 received a ventricular-peritoneal shunt). The pathologic reports of tissue biopsy (Fig. 3) exhibited apple-green birefringence of amyloid under polarized

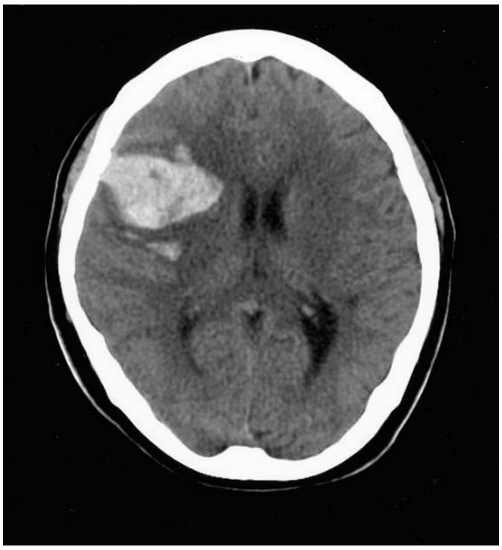

Figure 1. The initial brain CT in Patient 5 showed presence of a hyperdense hemorrhage in mainly the subcortical area of right frontoparietal region with mass effect causing narrowing of adjacent sulci and ventricle.

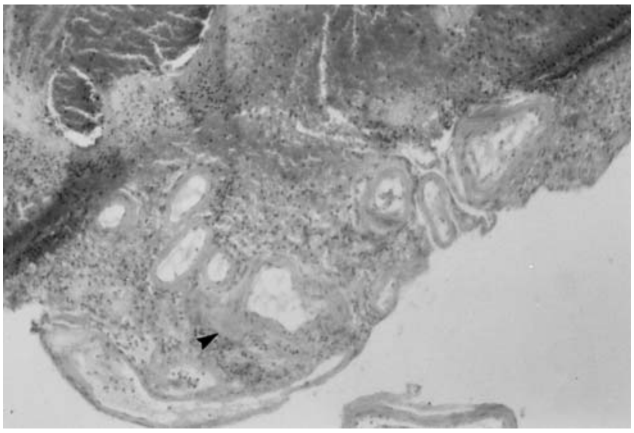

Figure 3. In Patient 3, the section of the specimen showed deposits of amyloid, an acellular eosinophilic material, within the vessel wall (hematoxylin and eosin, x100).

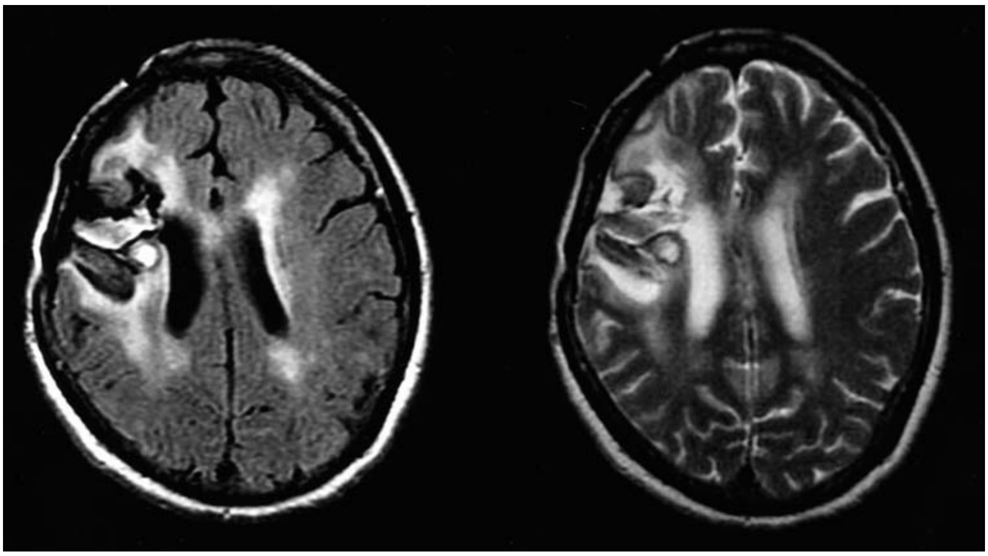

Figure 2. The brain MRI of Patient 5 with recurrent LICH revealed presence of ICH combined with hemosiderin and brain tissue loss change in the right side fronto- temporal and parietal region. Post-craniotomy in the right side fronto-parietal region was noted.

light and Congo-red stain. Considering the prognosis of our patients, the mean Rankin scale showed an average score of 3.4 without any mortality. However, three patients experienced recurrent hemorrhages with intervals between 5 days to 2.1 years.

DISCUSSION

Although the incidence of ICH is 29% of all acute strokes in southern Taiwan[3], it is more fatal than cerebral infarction. LICH comprised one third of all primary ICH, with the incidence increasing markedly with age. CAA was a common cause of sporadic LICH in aged patients, particularly in those without hypertension. A previous study estimated that more than one third of those aged 60-97 have CAA, and some appeared to have ICH or Alzheimer's disease[4].

CAA-related LICH is more often located at multiple lobes, particularly in frontal and parietal lobes. Rebleeding after the first LICH is not uncommon, especially resulting from amyloid angiopathy[1]. Patients with CAA-related LICH have a lower mortality rate and a greater risk of recurrence than those with hypertensive ICH. Hypertension may exacerbate the tendency to have CAA-related hemorrhage and vice versa. Control of blood pressure after the first hemorrhage may prevent ICH recurrences[5].

Regarding pathogenesis, CAA refers to the deposition of (beta)-amyloid protein in the media and adventitia of the blood vessels of the cerebral cortex and leptomeninges[6]. It narrows the vascular lumen and elicits the formation of microaneurysms. Therefore, it contributes to the development of ICH. Simultaneously, it inhibits vascular contractions and blocks homeostasis.

Current diagnosis of CAA has not yet been validated, but the Boston Criteria is used as a guideline. It classifies CAA into four levels. The "Definite" level means a case with pathologic confirmation by postmortem autopsy. The second level points to a "probable" case with clinical data and pathologic evidence. The third level means a "probable" case with clinical data and multiple hematomas on MRI. The final level describes a "possible" case with clinical data and a single lobar hematoma on MRI finding[7].

For early diagnosis of CAA-related LICH, gradient-echo MRI has been recommended to detect previous petechial hemorrhages with hemosiderin deposition. Follow-up gradient-echo MRI can investigate the possibility of recurrent hemorrhage. As many as 38% of patients with CAA have recurrent hemorrhages and are detected by this technique within 1.5 years after the first hemorrhage[8-9]. This kind of approach provides a noninvasive method for early diagnosis of small LICH and further evaluation of CAA progression.

CAA pathology has been seen in the form of pink hyaline thickening of arteries with narrowing of the lumen on Hematoxylin-eosin stain, but the most reliable finding is apple-green birefringence of amyloid under polarized light using Congo-red stain[10]. CAA is more closely associated with Alzheimer's disease, but is also seen in non-demented patients.

So far, CAA remains untreatable; even treatments aimed at the prevention of recurrent hemorrhage in patients with CAA-related LICH are not available. Previous studies have compared medical treatment alone with surgical hematoma evacuation. The initial cognitive condition (progressive deterioration of the level of consciousness) and hematoma volume (20 to 60 ml) of the patients with ICH have to be established as indicators for to surgery. Craniotomy with hematoma evacuation is of benefit in situations where there are severe mass effects, intraventricular hemorrhage(IVH) and increased intracranial pressure. The presence of blood in the ventricles is associated with a high mortality rate. This effect may be associated with the evolution of obstructive hydrocephalus. External drainage of cerebrospinal fluid through ventricular catheters reduces intracranial pressure[11]. Some authors describe the use of a soluble hemostat to control rebleeding during the operation. A previous study[12] suggested surgical management for CAA-related LICH, because post-operation hemorrhage (POH), which means recurrent hemorrhage within 48 hours after operation, makes for a low mortality rate and does not negatively influence the outcome for the patients. Risk factors for an adverse postoperative outcome are parietal hematomas, advanced age, and IVH[12]. In our study, three patients had suffered from rebleeding, proximal to the first bleeding sites. All the rebleeding event intervals exceeded 48 hours, so the mechanism of rebleeding may be due to causes other than surgical techniques.

To predict the prognosis of sporadic LICH, some authors have documented a low score on the Glasgow Coma Scale, a large volume of the hematoma (>60 ml), and the presence of ventricular blood on the initial CT scan as the factors that contribute to a high mortality rate[2]. O'Donnell et.al. have demonstrated that an apolipoprotein E (APOE) gene consisting of epsilon 2 and epsilon4 alleles might be clinically useful in assessing a patient's prognosis with respect to recurrent lobar hemorrhage[13]. But the data accounts for recurrent rather than initial hemorrhage. The APOE genotype is neither sensitive nor specific for the initial diagnosis of CAA. One study revealed that 33 % of patients with pathologic evidence of CAA-related LICH did not have the APOE genotype (epsilon 2 or 4).

In certain clinical conditions when treatments such as anticoagulation or thrombolysis are under consideration, diagnosis of CAA may influence the decision, especially in aged patients[14]. Although diagnosis of CAA before hemorrhage is not established, it is important to identify the patients at high risk for LICH before initiation of anticoagulant therapy in the future.

The five cases in our article had a mean age of 76 years, so they belong to the group at high risk for CAA. Only one (Patient 3) had a history of hypertension, and this predisposing factor seemed associated with his poor outcome. Clinical features consisted of various neurological symptoms such as headache, limb weakness, seizure or altered consciousness, but no Alzheimer's dementia. As to the seizure attack of Patient 5, we supposed it was precipitated by the LICH, because most seizures occur at the onset or within the first 24 hours of ICH[15]. Craniotomy with or without ventricular catheterization depended on the location and size of the hematoma, the presence of ventricular blood, and the occurrence of hydrocephalus on the initial CT scan. Recurrent hemorrhage had ensued, with variable severity of outcomes for Patient 1, 3 and 5, and particularly in Patient 3, who had three instances of recurrent LICH within six months. We identified the patient's hypertension as an adverse factor. Although the APOE genotype had not been identified in all cases, it might have shown a great impact on the recurrent LICH. We agree with the decision to do craniotomy with hematoma evacuation under situations of initial consciousness level, with IVH, and hematoma size. The five patients were discharged with severe neurological deficits. However, a lower mortality in these patients existed despite the frequency of LICH.

In summary, CAA is a significant risk factor for sporadic LICH in aged patients. To our knowledge, specific treatment is not currently available, but surgery for decompression of increasing intracranial pressure is reasonable and life saving. At present, it is possible to develop the gradient-echo MRI imaging for early diagnosis of CAA-related LICH.

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