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Clinical and neuropathologic analysis of intracerebral hemorrhage in patients with cerebral amyloid angiopathy☆

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ABSTRACT

Objective: To evaluate the clinical and histopathological features of elderly patients with subcortical intracerebral hemorrhage (ICH), and to analyze the presence of cerebral amyloid angiopathy (CAA) and Alzheimer's disease (AD) type pathologic changes using amyloid beta (Aβ) and tau immunohistochemistry.
Patients and methods: We retrospectively analyzed cases satisfying the Boston criteria for CAA among patients with subcortical hemorrhage who underwent surgical removal by craniotomy at our hospital. Surgical specimens were subjected to hematoxylin and eosin (HE) staining as well as immunostaining.
Results: A total of 54 patients were included in this study, with a mean age of 74.5 years (range: 72.5–76.5 years, 95% confidence interval [CI]; 51% female). Of these 54 patients, 31 (57%) were hypertensive, 18 (33%) were undergoing antithrombotic therapy, and 12 (22%) had dementia. Strong immunoreactivity for Aβ40 in the cerebral vessels was observed in 30 patients (55.6%), and among these, 27 patients (90%) also showed strong immunoreactivity for Aβ42. Among the 54 patients, 25 (46%) exhibited AD characteristics, including Aβ-positive senile plaques and AT8-positive neurons. Multivariate analysis revealed that strong Aβ40 immunoreactivity in the cerebral vessels was associated with older patients, females, lack of high blood pressure, and the presence of AT8-positive neurons.
Conclusion: CAA patients with strong Aβ40 deposition in the cerebral vessels were associated with subcortical hemorrhage in our cohort. Future studies should investigate the pathomechanism of ICH in individuals with CAA.

1. Introduction

There has been a great amount of scientific interest in the relationship between cerebral amyloid angiopathy (CAA) and Alzheimer's disease (AD) [1–3]. In general, CAA is a well-known major cause of spontaneous intracerebral hemorrhage (ICH) in the elderly. In AD, the deposition of amyloid beta (Aβ) is present in the cerebral parenchyma and cerebral blood vessels of the cortex and leptomeninges. Senile plaques mainly consist of Aβ42, while in CAA, Aβ40 is the predominant form in the deposits, with Aβ42 a minor component. Some studies have suggested that the progression of CAA parallels an increase in Aβ40 deposition [4,5]. However, these previous studies did not examine the link between CAA-related ICH (CAA-ICH) and AD. In clinical practice, many aged individuals with cerebral hemorrhage have a history of dementia including AD. Therefore, it is important to clarify the pathologic condition of cerebral hemorrhage from the perspective of CAA and AD pathologic changes.

The aim of the present study was to evaluate the clinical and histopathological features of elderly patients with subcortical ICH, and to elucidate the relationship between CAA-ICH and AD type pathologic changes using surgical specimens.

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; NFT, neurofibrillary tangle

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2. Materials and methods

2.1. Study design

The present study was a retrospective analysis of collected data from patients who underwent evacuation of lobar ICH at a single institution (Saitama Medical University International Medical Center, SIMC). The SIMC was established as a tertiary teaching hospital in 2007, and is located in the western Saitama Prefecture in Japan. Our department handles 30–40 patients with acute hemorrhagic stroke each day.

In this paper, the following will be discussed: (1) the clinical characteristics of the whole group; (2) pathologic assessment by hematoxylin and eosin (HE) staining and immunostaining of the surgically evacuated brain tissue; and (3) the clinical and histopathologic characteristics of the group with strong immunoreactivity for Aβ40 in cerebral vessels (indicative of Aβ40 deposition). This study was approved by the SIMC Institutional Review Board (15–248).

2.2. Patient selection

A total of 101 consecutive patients underwent surgical removal of subcortical ICH at our hospital from April 2010 to December 2015. Of these patients, we identified those who met the following Boston criteria for CAA: (1) age over 55; and (2) absence of other causes of hemorrhage. “Other causes” were defined as excessive warfarin (INR > 3.0), antecedent head trauma or ischemic stroke, CNS tumor, vascular malformation, vasculitis, blood dyscrasia, or coagulopathy (Fig. 1). [6]

At the time of hematoma removal, we submitted the tissue samples for routine pathologic examination. We excluded subjects with samples not containing any vessels or cerebral parenchyma. A total of 54 patients were eligible for study inclusion and analysis. Among the 54 patients, one patient with Down’s syndrome was included.

2.3. Clinical data collection

We retrospectively collected clinical and neuroimaging data from electronic medical charts and discharge summaries. The following clinical data were collected for each patient: age, sex, systolic/diastolic blood pressure on admission, HbA1c score, sum of the Glasgow Coma Scale (GCS) on admission, modified Rankin Scale (mRS) at the time of discharge, and history of hypertension, diabetes, dementia and antithrombotic therapy. History of hypertension, diabetes and dementia were defined as current use of anti-hypertension or anti-diabetes or anti-dementia medications.

2.4. Neuroimaging data

Hematoma volume, hematoma locations, existence of intraventricular hemorrhage (IVH) and subarachnoid hemorrhage (SAH) on last computed tomography (CT) scan before surgery, and re-bleeding after surgery were confirmed by neuroradiologists. Hematoma volume was calculated using the ABC/2 technique [7], where A is the maximum diameter of the hemorrhagic area, B is the diameter at 90° to A, and C is the number of CT slices with hemorrhage multiplied by the slice thickness. Hematoma locations were evaluated by dividing the area where the hematoma was distributed in the frontal lobe, parietal lobe, temporal lobe, and occipital lobe. When the hematoma spanned multiple adjacent lobes, it was recorded as bleeding in each lobe.

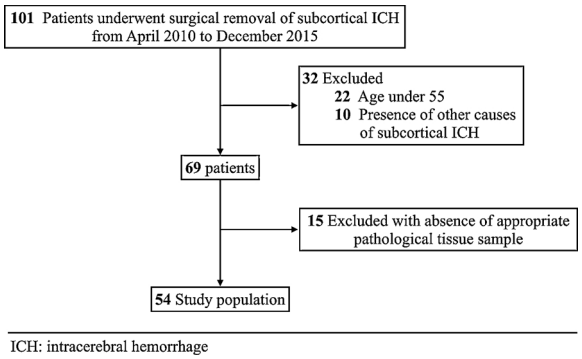

Fig. 1. Details of patient selection.

2.5. Pathologic data collection

Neuropathological studies were carried out on the remaining specimens at the time of hematoma evacuation from each individual. Blocks were dehydrated in a graded alcohol series, cleared in xylene, and embedded in paraffin. The brain tissues were cut into 6-μm-thick sections and stained with HE. For immunohistochemical studies, monoclonal antibodies specific to Aβ11–28 (12B8, IBL, Gunma, Japan; 1:100), Aβ35–40 (1A10, IBL; 1:100) and phospho-tau (Ser202, Thr205) (AT8; Innogenetics, Ghent, Belgium; 1:3000), as well as a polyclonal antibody specific to Aβ1–42 (IBL; 1:100), were used. The sections were processed using a Ventana Discovery automated immunostainer (Roche, Basel, Switzerland) and the sections were counterstained with hematoxylin. Immunostaining was performed on serial sections and the degree of immunostaining of the same blood vessels was investigated. In particular, the number of vessels immunoreactive (positive) for Aβ35–40 were counted in the section. If the percentage of immunoreactive vessels was 80% or more, the case was assigned to group A (defined as strong immunoreactivity). The remaining cases were assigned to group B. Here, the immunoreactive vessels were defined as those with Aβ35–40-immunoreactive deposits in the vessel walls, entirely and circumferentially. Partially immunoreactive vessels were considered negative in this study.

We also analyzed the presence of Aβ-immunoreactive senile plaques (Aβ42 or Aβ11–28) and AT8-immunoreactive cortical neurons (including neurofibrillary tangles and pretangles) or neuropil threads. In particular, neuritic plaques were identified using Aβ and AT8 immunohistochemistry. Because the study was carried out using surgically evacuated tissue, we were not able to study the distribution of senile plaques or neurofibrillary tangles.

2.6. Statistical analysis

The age, hematoma volume, and systolic/diastolic blood pressure on admission were analyzed by Student’s *t*-test. HbA1c score, sum of the GCS on admission, and mRS at the time of discharge were analyzed with the Mann-Whitney *U*-test. Sex, history of hypertension, diabetes, dementia, antithrombotic therapy, existence of IVH, SAH on last computed tomography (CT) scan before surgery, and re-bleeding after surgery were analyzed using Pearson’s $\chi 2$ or Fisher’s exact test. Stepwise logistic regression was used to identify confounders with the presence of Aβ deposition as an outcome, and all other variables as independent variables. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics

Table 1 shows a summary of the patient data. The patients in this study had a mean age of 74.5 years (range: 72.5–76.5, 95% CI). The mean age of 28 females was 75.5 years. The mean age of 26 males was 73.5 years, and there was no significant difference between the sexes ($P = 0.32$).

Among the 54 patients, 31 (57%) had a history of hypertension, 4 (7.4%) had a history of diabetes, 12 (22%) had pre-existing dementia,

Table 1
Characteristics of the study population.

	total cohort (N = 54)	Group A (n = 30)	Group B (n = 24)	P value
character				
Age,mean (95%CI), y	74.5(72.5-76.5)	77.3(74.7-80.0)	68.7(64.4-73.1)	0.008
Female, No. (%)	28(51.9)	23(76.7)	5(20.8)	< 0.001
Hypertension, No. (%)	31(57.4)	11(36.7)	20(83.3)	0.001
Diabetes, No. (%)	4(7.4)	0	4(16.6)	0.02
Dementia, No. (%)	12(22.2)	11(36.7)	1(4.2)	0.004
Antithrombotic therapy, No. (%)	18(33.3)	5(16.7)	13(54.2)	0.004
systemic factor				
Systolic blood pressure, Mean (95%CI), mmHg	176(167-186)	163(146-180)	194(175-213)	0.139
Diastolic blood pressure, Mean (95%CI), mmHg	84.7(78.6-90.8)	71.2(63.9-78.5)	97.7(80.9-114)	0.121
HbA1c, Mean(95%CI)	5.7(5.5-5.9)	5.6(5.4-5.8)	6.1(5.5-6.7)	0.272
Sum of GCS score, Median (IQR)	9.5(7-12)	10(8-13)	9(6-12)	0.995
mRS at the time of discharge, Median (IQR)	4(4-5)	4(3.5-4.5)	4(4-5)	0.206
CT factors				
Hemorrhage volume, median(IQR), mL	82(55-99)	66(59-104)	87(70-96)	0.831
with IVH, No. (%)	16(27.7)	7(23.3)	9(37.5)	0.257
with SAH, No. (%)	25(46.3)	14(46.7)	11(45.8)	0.951
rebleeding, No. (%)	16(29.6)	6(20)	10(41.7)	0.083
pathology				
Neuritic plaque (Aβ42), No. (%)	44(81.5)	26(86)	18(75)	0.228
(Aβ11-28), No. (%)	43(79.6)	28(93)	15(62.5)	0.007
AT8 deposition to central nerve cells, No. (%)	29(53.7)	24(80.0)	5(20.8)	< 0.001

CI = confidence interval; GCS = Glasgow Coma Scale; IQR = interquartile range; mRS = modified Rankin Scale; IVH = intraventricular hemorrhage; SAH = subarachnoid hemorrhage.

and 18 (33%) were undergoing antithrombotic therapy. Among the latter, 12 patients were taking antiplatelet drugs, 5 were taking anticoagulants, and 1 was on both medications.

Non-contrast CT scan was taken for all 54 cases, but contrast enhanced CT scan was taken for only 24 (44%) cases. MRI was taken before surgery in nine cases, and after surgery in 22 (41%) cases. In 17 (31%) cases, neither contrast enhanced CT nor MRI were taken. T2* images were taken in 13 cases, and microbleeds were present in six of these. [8,9] The locations of hematoma judged by CT exam were as follows: 33 cases, frontal lobes; 32 cases, temporal lobes; 30 cases, parietal lobes; and 15 cases, occipital lobes. For hematomas spanning multiple lobes, we separately counted each lobe. There were no dominant regions for hemorrhage in the present study. All cases were considered typical hemorrhage as judged by CT scan. The median ICH volume was 82 ml, ranging from 30 to 159 ml. Among 54 cases, 16 (30%) had IVH, 25 (46%) had SAH, and 8 (15%) had both. Based on CT images, 16 (30%) cases exhibited re-bleeding (including small bleed). Among these, 4 (25%) were symptomatic. The median mRS at the time of discharge was 4, and 5 (9.3%) patients had mRS 0–2 at the time of discharge.

3.2. Histopathologic assessment of surgically evacuated tissue

Aβ35–40 deposits in the cerebral vessels were seen in 30/54 (56%) patients, and were absent in 24/54 (33%) patients (which included cases of partially immunoreactive Aβ35–40 deposits in the vessel walls). Strongly Aβ42-immunoreactive deposits in the cerebral vessels were seen in 31/54 (57%) patients, and were absent in 23/54 (35%) patients. Strong immunoreactivity for Aβ40 and Aβ42 was present in 27/54 (50%) patients. Therefore, three cases strongly positive for Aβ40 were negative for Aβ42. Conversely, four cases strongly positive for Aβ42 were negative for Aβ40.

Strongly Aβ11–28-immunoreactive deposits in the cerebral vessels were present in 34/54 (63%) patients, and 27/54 (50%) patients showed strong immunoreactivity with all three—Aβ40, Aβ42 and Aβ11–28—antibodies. Of the 54 patients, 15 (28%) showed no immunoreactivity for Aβ40, Aβ42, or Aβ11–28. Aβ42- and Aβ11–28-immunoreactive plaques were seen in 44/54 (81%) and 43/54 (80%) patients, respectively. Representative photomicrographs are shown in Fig. 2.

AT8-immunoreactive neurons, including neurofibrillary tangles and pretangles, as well as neuropil threads, were found in 29/54 (54%) cases (Fig. 3). In the sections analyzed, there was no fibrinoid degeneration or microaneurysms that are occasionally found in the cerebral parenchyma of individuals with hypertensive cerebral hemorrhage.

3.3. Comparison of clinical and imaging characteristics between groups A and B

Patient characteristics are summarized in Table 1. Group A was older (mean age of 77.3 vs 68.7, $P = 0.008$), with a higher percentage of females (77% vs 21%, $P < 0.001$) and a higher percentage of patients with dementia (37% vs 4.2%, $P = 0.004$), compared with group B. Group B had a higher percentage of patients with a history of hypertension (37% vs 83%, $P = 0.001$) and diabetes (0% vs 17%, $P = 0.02$). There were fewer patients undergoing antithrombotic therapy in group A than in group B (17% vs 54%, $P = 0.004$). The two groups had similar hemorrhage volumes and sums of the GCS score on admission and mRS at the time of discharge. Systolic/diastolic blood pressure on admission was similar in the two groups, although a history of hypertension was more frequent in group A than in group B ($P = 0.001$). The prevalence of diabetes was low in both groups. In particular, no diabetes case was present in group A.

There were no significant differences in Aβ40- or Aβ42-immunoreactive parenchymal deposits. However, senile plaques with Aβ11–28 immunoreactivity were frequently seen in group A ($P = 0.007$). AT8-immunoreactive neurons and neuropil threads were also more numerous in group A than group B ($P < 0.001$). Multivariate analysis was carried out for items with significant differences in univariate analysis. The results of multiple logistic regression analysis by backward elimination (Wald) are shown in Tables 2 and Table 3. The item “diabetes” was not included in the analysis because group A contained no cases of diabetes. In multivariate analysis, significant differences were found in four items.

4. Discussion

One of the major aims of this study was to examine the clinical and

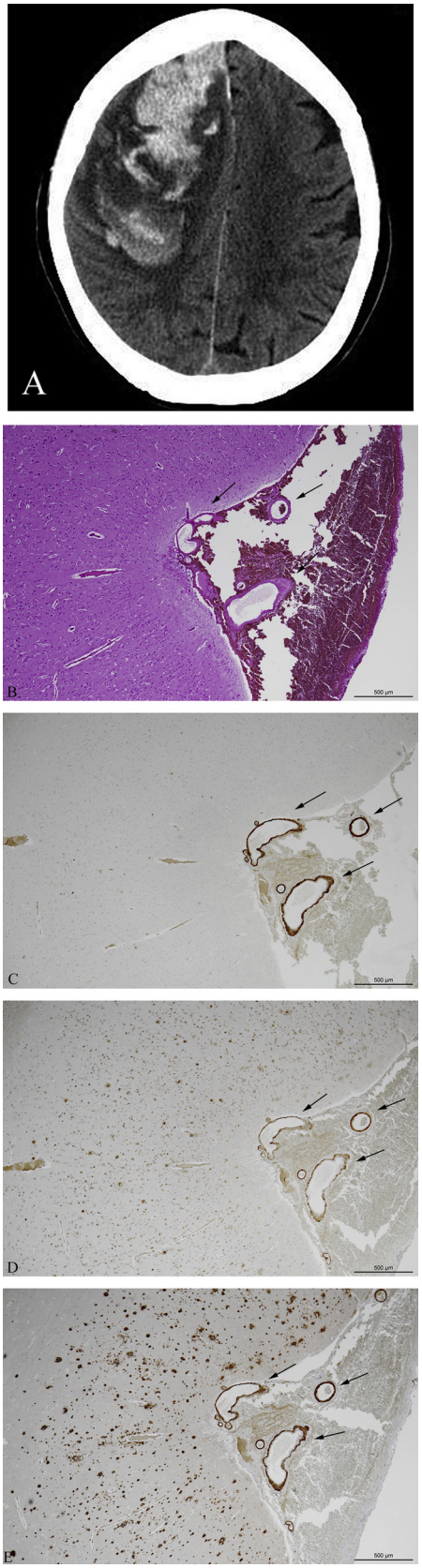

Fig. 2. A: A non-contrast computed tomographic axial image is shown for a 78-year-old patient demonstrating a large frontal acute intracerebral hemorrhage. B: Sections of the evacuated hematoma showing brain parenchyma and vessels with intimal thickening (arrows) (HE). C: Aβ40 immunoreactivity in vessel walls confirming the presence of cerebral amyloid angiopathy (CAA) (arrows). D and E: Prominent Aβ-immunoreactive senile plaques and CAA vessels are seen (arrows) (Aβ42 and Aβ11–28).

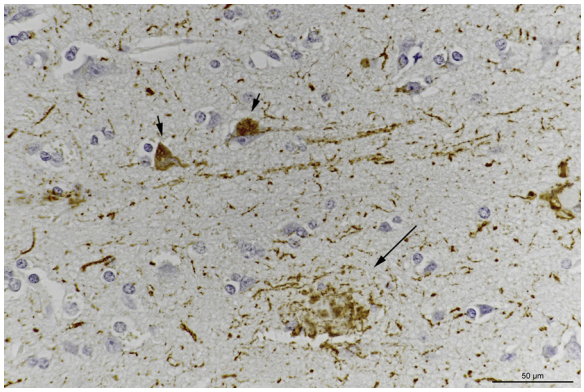

Fig. 3. AT8-positive neurofibrillary tangles and neuritic plaques. This panel demonstrates neurofibrillary tangles (short arrows) and neuritic plaques (long arrows) stained for AT8.

Table 2
Immunohistochemistry findings for the patients in this study.

Aβ40 deposition to cerebral vessels, number. (%)	30(55.6)
Aβ42 deposition to cerebral vessels, number. (%)	31(57.4)
Aβ40 and Aβ42 deposition to cerebral vessels, number. (%)	27(50.0)
Aβ11-28 deposition to cerebral vessels, number. (%)	34(63.0)
Aβ40 deposition to neuritic plaque, number. (%)	15(27.8)
Aβ42 deposition to neuritic plaque, number. (%)	44(81.5)
Aβ11-28 deposition to neuritic plaque, number. (%)	43(79.6)
AT8 deposition to central nerve cells, number. (%)	29(53.7)

Table 3
Logistic regression analysis for strongly Aβ40-positive deposits.

	Adusted OR (95%CI)	P Value
Age	1.316(1.028-1.685)	0.03
Female	0.028(0.001-0.620)	0.024
Antithrombotic therapy	27.9(0.939-828.9)	0.054
Dementia	1.55(0.064-37.36)	0.073
Hypertension	31.84(1.251-810.3)	0.036
Neuritic plaque (Aβ11-28)	0.192(0.003-14.13)	0.452
AT8(+) neural cell	0.060(0.005-0.751)	0.029

histopathological features of elderly patients with massive subcortical ICH. In other studies on hypertensive ICH, the mean age was 65–70 years, the percentage of women was about 40%, and the proportion of patients with hypertension and diabetes was about 80% and 15%, respectively [10,11]. Compared with these previous reports, the patients in this study were older and included a higher percentage of women. In comparison, the percentages of patients with hypertension and diabetes in this study were lower. There was no apparent difference in the rate of antithrombotic drug use compared with other reports [7,10,11]. In contrast, in other studies on subcortical ICH, the mean age was 70–75 years, females comprised 50–55% of the cases, and the proportion of hypertensive patients was 50–60% [12–15]. Therefore, the clinical backgrounds of our cases are similar to those of the relatively old populations that were previously reported.

There was no specific tendency in hematoma volume or hematoma location. The low sum of the GCS scores on admission suggests that the poor outcome was a result of severe initial damage. Table 2 summarizes the immunostaining results for cerebrovascular and senile plaques. We cannot conclude that the 18 cases that were Aβ40-immunonegative were not CAA. To confirm that the cause of hemorrhage was not CAA, brain autopsy is necessary. However, the findings suggest that the cause of hemorrhage in these 18 cases was not associated with hypertension. Indeed, we did not see any small vessel pathology such as fibrinoid necrosis or microaneurysms.

Most reports suggest that CAA is mainly associated with Aβ40

deposition. Justin et al. examined surgically removed specimens from 20 patients with ICH [15]. In their study, Aβ40 staining demonstrated CAA in 8/20 patients (40%). In comparison, more than 50% of the CAA cases were associated with Aβ40 deposition in the present study, using a very strict definition of immunoreactivity towards Aβ. Therefore, CAA is likely to be an important cause of cerebral hemorrhage in the elderly.

In this study, blood vessels immunoreactive for Aβ40 were often immunoreactive for Aβ42 and Aβ11–28 as well, as shown in Fig. 2. Many patients had deposition of both Aβ42 and Aβ40 in their cerebral vessels. Differences in clinical characteristics between cases positive for Aβ40 and other cases were not observed in this study. Because our histopathologic analysis was limited to surgically evacuated tissue, additional biochemical studies may reveal differences in Aβ isoforms in the blood vessels and cerebral hemorrhages.

Senile plaques containing Aβ42-positive deposits and AT8-positive neurons are characteristic pathological features of AD, and are often observed before the clinical manifestation of AD [16]. Although a neuropathologic diagnosis must be autopsy-based, we speculate that some cases with Aβ-immunoreactive senile plaques and AT8-immunoreactive neurons on surgical specimens may reflect AD pathology. There were 25 cases with Aβ-positive senile plaques and AT8-positive neurons. In addition, 10 of these 25 cases had a medical history of dementia according to the medical chart on admission. Neuropathologically, nine cases had strongly immunoreactive CAA (group A) and one had mildly immunoreactive CAA (group B). Therefore, some cases of subcortical hemorrhage with CAA may be associated with AD pathologic changes. This is in line with a recent study showing that neuritic plaques in isolation (without neurofibrillary tangles) were more frequent in CAA patients with ICH than those without ICH [11].

However, for the neuropathologic diagnosis of AD, the severity and distribution of Aβ-positive senile plaques and tau immunoreactive neurofibrillary tangles must be analyzed in many anatomical areas [17]. Therefore, we are not able to conclude that these CAA cases are also AD.

Another major finding of the present study is that group A had more women and was older than group B. This result was supported by the logistic regression analysis. In general, hypertension, diabetes, and antithrombotic therapy are associated with ICH. [18] APOE ε2, hypertension, antithrombotic therapy, and head trauma have been reported as risk factors [14,19–22].

In the present study, group A had a lower percentage of patients with a history of hypertension, diabetes, and antithrombotic therapy compared with group B. Among the 54 cases, 18 had no apparent history of any of these three risk factors. In particular, 15 (83%) of these 18 cases were in group A, where even if the risk of bleeding was low, it tended to cause massive ICH. These findings, together with the logistic regression analysis, suggest that CAA is an important risk factor for subcortical hemorrhage in the elderly.

Several limitations of this study should be acknowledged. First, we did not investigate genetic factors, such as APOE genotype. A further study of the relationship between Aβ40 deposition and APOE genotype should be conducted. Second, the study size was small. Third, there was potential selection bias because the intraoperative specimens were obtained from only one institution. Because the number of MRI cases was limited, future prospective analysis needs to be carried out for imaging and pathologic correlations.

5. Conclusion

We performed a neuropathologic analysis using surgical specimens from aged patients with ICH. Together, our findings suggest that: (1) CAA patients with massive ICH are more likely to be female and older; (2) some ICH patients with CAA may have associated AD pathologic changes; and (3) CAA patients with strong Aβ40 deposition in the cerebral vessels are associated with subcortical hemorrhage compared with those having well-known risk factors such as hypertension. Our findings may help develop future treatment strategies for patients with CAA. Future studies should investigate the pathomechanism of ICH in individuals with CAA.

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