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Study of clinical features of amyloid angiopathy hemorrhage and hypertensive intracerebral hemorrhage

ZHAN Ren-ya (詹仁雅)[†1], TONG Ying (童 鹰)[1], SHEN Jian-feng (沈剑峰)[1], LANG E.[2], PREUL C.[2], HEMPELMANN R.G.[2], HUGO H.H.[2], BUHL R.[2], BARTH H.[2], KLINGE H.[2], MEHDORN H.M.[2]

([1]*Department of Neurosurgery, First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China*)

([2]*Department of Neurosurgery, Kiel University, Kiel D-24106, Germany*)

[†]E-mail: ZRY1960@hzcnc.com

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Abstract: Objective: The purpose of this study was to differentiate between cerebral amyloid angiopathy (CAA) and hypertension (HTN) based on hemorrhage pattern interpretation. Methods: From June 1994 to Oct., 2000, 83 patients admitted to our service with acute intracerebral hemorrhage (ICH) were investigated retrospectively; 41 patients with histologically proven diagnosis of cerebral amyloid angiography and 42 patients with clear history of hypertension were investigated. Results: Patients with a CAA-related ICH were significantly older than patients with a HTN-related ICH (74.0 years vs 66.5 years, $P<0.05$). There was a significantly higher number of hematomas≥30 ml in CAA (85.3%) when compared with HTN (59.5%). No basal ganglional hemorrhage was seen in CAA, but in 40.5% in HTN. In CAA-related ICH, subarachnoid hemorrhage (SAH) was seen in 26 patients (63.4%) compared to only 11 patients (26.2%) in HTN-related ICH. Intraventricular hemorrhage was seen in 24.4% in CAA, and in 26.2% in HTN. Typical features of CAA-related ICH included lobar distribution affecting mainly the lobar superficial areas, lobulated appearance, rupture into the subarachnoid space, and secondary IVH from the lobar hemorrhage. More specifically, multiplicity of hemorrhage, bilaterality, and repeated episodes also strongly suggest the diagnosis of CAA. Multiple hemorrhages, defined as 2 or more separate hematomas in multiple lobes, accounted for 17.1% in CAA-related ICH. Conclusion: There are certain features in CAA on CT and MRI and in clinical settings. To some extent, these features may contribute to distinguishing CAA from HTN related ICH.

Key words: Intracerebral hemorrhage, Cerebral amyloid angiopathy, Hypertension, Diagnosis, Computed tomography, Magnetic resonance imaging

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INTRODUCTION

It is commonly felt that CAA-related ICH can be distinguished from HTN-related ICH by certain typical features on CT and MRI. On one hand the location of the hematomas, affecting mainly the lobar superficial areas, a predominant involvement of the cortex and the frequent extension of blood into the subarachnoid space, and, on the other hand a lobulated or irregularly shaped appearance may suggest the diagnosis of CAA, especially if there are multiple hematomas. In contrast, HTN-related ICH frequently involves the basal ganglia and thalamic regions, the pons and the cerebellum. Amyloid angiopathy almost never involves these structures.

Surgical treatment of ICH caused by amyloid angiopathy remains controversial. Several reports

indicated that surgery of CAA-related hematomas often involve difficulties in controlling intraoperative bleeding. In addition the possibility of recurrent postoperative hemorrhage is increased in patients with CAA-related hemorrhage. It would therefore be desirable to distinguish between CAA and HTN-related hemorrhage, ideally before surgery, based on neuroimaging. The purpose of this study was to investigate clinical features of amyloid angiopathy hemorrhage and hypertensive intracerebral hemorrhage.

METHODS

Eighty-three patients who were treated with an acute CAA or HTN-related ICH from Jun. 1994 to Oct. 2000 were investigated. All clinical records and their CT scans or MRI were reviewed and analyzed regarding age, gender, and presence of ICH.

Group I, the CAA group, consisted of 41 patients with CAA-related ICH; 17 patients (41.5%) had a history of HTN in this group. Microsurgical hematoma evacuation was done in all CAA patients and CAA was histopathologically confirmed as the cause of hemorrhage by brain tissue specimens which were obtained from the tissue adjacent to the hemorrhage. Hematoma evacuation was performed for the following indications: significant mass effect; non-eloquent brain region; favorable prognostic factors such as no or minor accompanying disease; and acute deterioration.

Group II, the HTN group, consisted of 42 patients with HTN-related ICH; HTN was considered present if there was a clear history of HTN documented in the admission note. If such diagnosis was not known upon admission but later confirmed by the patient's general practitioner, or if the diagnosis of HTN was previously unknown and the patient was discharged with antihypertensive medication. Hematoma evacuation was done using open microsurgical techniques in 59.5% of HTN patients (n=25) and a histopathological diagnosis excluding CAA was obtained.

The location of each hematoma was defined according to the lobe in which it was predominantly located. Its location was classified as lobar (frontal; parietal; occipital; temporal), basal ganlionic/thalamic or cerebellar. For cases of multiple lobar hemorrhages, which was defined as two or more separate hemorrhages in multiple lobes, the largest hematoma was examined. Hematomas were graded as "small" if they were smaller than 30 ml, "medium" if they were equal to or larger than 30 ml but smaller than 60 ml, and "large" if they were equal to or larger than 60 ml. Their shapes were arbitrarily described as round, lobular, or irregular. The presence of subarachnoid hemorrhage (SAH) and intraventricular hemorrhage (IVH) was also documented.

A statistically significant difference between CAA-related ICH and HTN-related ICH was observed for the following variables: 1) age; 2) hematoma locations; 3) hematoma shape; 4) hematoma size; 5) subarachnoid extension of the hematoma with secondary SAH; 6) intraventricular extension of the hematoma with secondary IVH. Chi-square test was used for statistical analysis. Probability values of <0.05 were considered statistically significant.

RESULTS

Age and gender

For both groups, there were 37 male and 46 female patients with age ranging from 44 years to 90 years, mean of 69.2±11.9 years. In group I, there were 20 male and 21 female patients with age ranging from 53 years to 90 years, mean of 74.0±8.0 years. In group II, there were 17 male and 25 female patients with age ranging from 44 years to 83 years, mean of 66.5±9.5 years. Patients in the CAA-related ICH group were significantly older than the HTN-related ICH group (P<0.05) (Table 1).

Location

In group I, hematomas were mainly classified as lobar hemorrhage (n=39, 95.1%); 14 hematomas (34.1%) were located in the parietal lobe, 12 hema-

Table 1 Age distribution of CAA and HTN related ICH

Age	40–49	50–59	60–69	70–79	80–89	>89
CAA	–	2 (4.9%)	10 (24.4%)	20 (48.8%)	8 (19.5%)	1 (2.4%)
HTN	3 (7.1%)	6 (14.2%)	14 (33.3%)	17 (40.5%)	2 (4.8%)	–
Total	3 (3.6%)	8 (9.6%)	24 (28.9%)	37 (44.6%)	10 (12.0%)	1 (1.2%)

CAA=cerebral amyloid angiopathy; HTN=hypertension; ICH=intracranial cerebral hemorrhage

tomas (29.3%) in the occipital lobe, 7 hematomas (17.1%) in the frontal lobe, 6 hematomas (14.6%) in the temporal lobe. There were 2 cerebellar hematomas (4.9%). Seven of 41 CAA-related ICH (17.1%) presented as multiple lobar hemorrhage. In group II, hematomas were classified as lobar bleeding in 18 cases (42.9%). Eight of 42 cases (19.0%) were located in the occipital, 6 cases (14.3%) were located in the parietal lobe, 2 cases (4.8%) were located in the frontal lobe and the temporal lobe, respectively. Seventeen cases (40.5%) were found in the basal ganglionic and thalamic region. Cerebellar hematomas were seen in 7 cases (16.7%) in HTN-related ICH. There were significant more cases with lobar hemorrhage in CAA-related ICH than HTN-related ICH (P<0.05) and there were significant more cases with basal ganglionic and thalamic hemorrhages in HTN-related ICH than CAA-related ICH (P<0.05). There was no significant difference in cerebellar hemorrhages (P>0.05) between CAA and HTN-related ICH (Fig.1).

Shape

In CAA-related ICH, 17 cases (41.5%) were lobular compared with 5 cases (11.9%) in HIT-related ICH (P<0.05). In CAA-related ICH 15 cases (36.6%) were irregular and 9 cases (22.0%) were round. In HTN-related ICH, 22 cases (52.4%) were irregular and 15 cases (35.7%) were round. There was no significant difference in irregular and round hemorrhages between CAA group and HTN group (P>0.05) (Table 2).

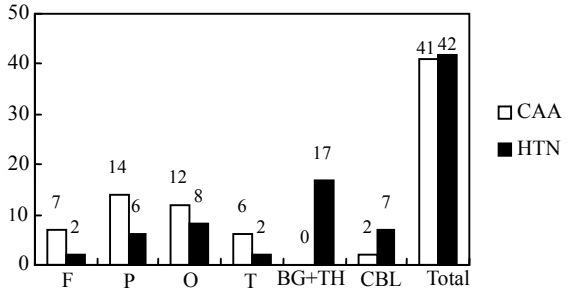

Fig.1 Locations of CAA and HTN related HTN related ICH

CAA=cerebral amyloid angiopathy; HTN=hypertension; F=frontal; P=parietal; O=occipital; T=temporal; BG+TH=basal ganglionic and thalamic; CBL=cerebellar

Size

In CAA-related ICH, 6 cases (14.6%) were small, 14 cases (34.1%) were medium, and 21 cases (51.2%) were large. In HTN-related ICH, 17 cases (40.5%) were small, 12 cases (28.6%) were medium and 13 cases (30.9%) were large. There was a significant difference for small hemorrhages between group I and group II (P<0.05). There was no significant difference for medium and large hemorrhages (P>0.05) between CAA and HTN (Table 3).

SAH and IVH

In CAA-related ICH, SAH was seen in 26 patients (63.4%) compared to only 11 patients (26.2%) in HTN-related ICH. This difference was statistical-

Table 2 Shape of CAA and HTN related ICH

Shape	CAA	HTN	χ^2
Irregular	15 (36.6%)	22 (52.4%)	2.1; P>0.05
Lobulated	17 (41.5%)	5 (11.9%)	9.3; P<0.05
Round	9 (22.0%)	15 (35.7%)	1.9; P>0.05
Total	41	42	

Table 3 The size of CAA and HTN related ICH

Size	CAA	HTN	χ^2
Small:<30 ml	6 (14.6%)	17 (40.5%)	6.9125; P<0.05
Medium: ≥ 30 ml; <60 ml	14 (34.1%)	12 (28.6%)	0.2997; P>0.05
Large: ≥60 ml	21 (51.2%)	13 (30.9%)	3.5239; P>0.05
Total	41	42	

ly significant ($P<0.05$). In CAA-related ICH all SAH cases were seen in lobar hemorrhage cases; 12 ICH were located in the parietal lobe, 8 in the occipital lobe, 3 in the temporal and 3 in the frontal lobe, respectively. We found no association between hematomas located in the basal ganglionic/thalamic regions or the cerebellum and SAH. In HTN-related ICH SAH cases, however, the locations of lobar ICH were: 3 in the occipital lobe, 2 in the parietal lobe, 1 in the temporal and 1 in the frontal lobe, respectively. Two ICH were located in the basal ganglionic/thalamic regions, and 2 in the cerebellum. In CAA-related ICH, IVH was seen in 10 patients (24.4%), and in 11 patients (26.2%) in HTN ($P>0.05$). All IVH ruptured from lobar hemorrhages in CAA, six ICH were located in the parietal lobe, 2 in the temporal lobe, 1 in the frontal and 1 in the occipital lobe, respectively. In HTN-related ICH, no IVH originated from lobar hemorrhage, 8 cases ruptured from basal ganglionic /thalamic ICH and 3 cases ruptured from a cerebellar hemorrhage into the ventricular system.

Intraventricular hemorrhage in combination with a lobar hematoma was only seen in CAA, which for those cases made the diagnosis of CAA almost certain; however this combination only applied to a small fraction of patients. At the same time IVH in combination with a deep-seated (basal ganglionic/thalamic) hematoma was a clear indication for a HTN-related ICH. Once again this combination only applied to a small fraction of all patients (Table 4).

DISCUSSION

CAA is considered the third most common cause of spontaneous intracerebral hemorrhage after HTN and subarachnoid aneurysmal hemorrhage. Itoh and Yamada (1997) demonstrated that among 101 cases with ICH found in 1000 consecutively autopsied cases, CAA-related ICH accounted for 10.9% of ICH. Based on evidence in the literature and based on our own series we established the characteristic features of ICH caused by amyloid angiopathy. These features, however, cannot be universally applied and the established criteria were probably not present in all cases. Lang (2001) showed that the overall average classification accuracy of five independent observers was 66.7% (range: 62.7%–69.9%). For this reason, we suggest that it is impossible to establish the diagnosis of CAA based on hemorrhage pattern interpretation alone. Histological examination of brain tissue obtained during surgery is still necessary to clearly establish the diagnosis of CAA-related ICH.

The cases found in the literature are single case reports (Awasthi *et al.*, 1991; Wakai *et al.*, 1992; Leblanc *et al.*, 1991). We are not aware of any reports of study which systematically addressed the clinical features of amyloiy angiopathy hemorrhage.

There were 20 male and 21 female patients with age ranging from 53 years to 90 years, mean of 74.0±8.0 years in 41 patients with CAA-related ICH and there were 17 male and 25 female patients with age ranging from 44 to 83 years, mean of 66.5±9.5 years in 42 patients with HTN-related ICH in our series. The mean age in CAA-related ICH was significantly older than in HTN-related ICH ($P<0.05$).

As we had expected, CAA-related ICH increased with age. Previous reports indicated that the incidence of ICH in patients with CAA increased

Table 4 SAH and IVH associated with location of ICH

Location	SAH			IVH		
	CAA	HTN	χ^2	CAA	HTN	χ^2
Lobar	26 (63.4%)	7 (16.7%)		10 (24.4%)	–	
BG+TH	–	2 (4.8%)		–	8 (19.1%)	
CBL	–	2 (4.8%)		–	3 (7.1%)	
Total	26 (63.4%)	11 (26.2%)	11.6359 ($P<0.05$)	10 (24.4%)	11 (26.2%)	0.0356 ($P>0.05$)

SAH=subarachnoid hemorrhage; IVH=intraventricular hemorrhage; ICH=intracranial cerebral hemorrhage; CAA=cerebral amyloid angiopathy; HTN=hypertension; BG+Th=basal ganglionic and thalamic; CBL=cerebellar

after the age of 50 years. It had also been reported that 5% occurred in the seventh decade, 43% in the eighth decade, and 57% in persons over 90 years old (Leblanc *et al*., 1991; Itoh and Yamada, 1997). In our series all patients with CAA-related ICH were older than 50 years, 39 patients (95.1%) were older than 60 years, 29 patients (70.7%) were older than 70 years, 9 patients (22.0%) were older than 80 years and 1 patient (2.4%) was older than 90 years.

Vonsattel *et al*.(1991) found a mean age of 73.7 years in their series of 17 cases. Our series is comparable with regard to age (74.0 years±8.0 years) in CAA-related ICH. CAA is generally considered a disease of the elderly, it is noteworthy that it also occurs in sixty to seventy years old patients (Izumihara *et al*., 1999). In our series, 30 patients (73.2%) were sixty to seventy years old. For the HTN group we found a mean age of 66.5 years; 33 patients (78.6%) were older than 60 years, 19 patients (45.2%) were older than 70 years, 2 patients (4.8%) were older than 80 years; 31 patients (73.8%) were sixty to seventy years old.

In histopathologically proven CAA-related ICH, more than 30% of patients showed mixed microangiopathic change indicative of a combination of HTN and CAA. Izumihara *et al*.(1999) reported that fifteen of 37 patients with CAA-related ICH (41%) had a history of HTN. Seventeen of 41 patients (41.5%) with CAA-related ICH had a history of HTN in our series. Although in our series CAA was histopathologically confirmed as the origin of hemorrhage, HTN undoubtedly might be a contributing factor in causing hemorrhage in patients with CAA because different pathological mechanisms might be at work at same time.

Passero *et al*.(1995) demonstrated that the risk of rebleeding seemed to be high if the hemorrhage occurred at the junction of the gray and white matter, which is typically considered a site of hemorrhage in CAA, in particular when arterial HTN was poorly controlled. CAA-associated vascular changes such as fibrinoid necrosis (degeneration) and microaneurysm formation of cortical vessels, which were similar to changes found in hypertensive patients, were also involved in the development of CAA-related ICH. CAA-related changes in the media of the arteries could lead to a predisposition to microaneurysm formation or rupture.

Deposition of amyloid proteins in the vascular wall of the small subarachnoid and cortical arteries with secondary hyaline 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 disintegrated artery itself. In some vessels, amyloid angiopathy and HTN fibrinoid degeneration coexist. HTN may increase the tendency to CAA-related hemorrhage. This overlap is probably one of the reasons why it is sometimes difficult to distinguish CAA from HTN-related ICH.

More specifically, multiplicity of hemorrhage, bilaterality, and repeated episodes also strongly suggest the diagnosis of CAA (Awasthi *et al*., 1991; Wakai *et al*., 1992; Hendricks *et al*., 1990). Multiple hemorrhage, which was defined as 2 or more separate hematomas in multiple lobes, account for 17.1% in CAA-related ICH. Two of 7 patients (28.6%) had bilateral hematomas in our series.

Deposition of amyloid in cerebral tissue occurs in three locations: 1) within neurons as a component of neurofibrillary tangles, 2) within the walls of leptomeningeal and cortical blood vessels, and 3) as an extension from the vessel wall into the brain parenchyma. Such conditions can coexist in the same patient and may be responsible for amyloid deposition within the walls of leptomeningeal and cortical blood vessels.

CAA predominantly affected the lobes while sparing the basal ganglia, thalamus, or brainstem, typically because the penetrating vessels supplying these structures were not involved in this vasculopathy. The hemorrhages usually located at the junction of the gray and white matter. CAA-related ICH (95.2%) were located in the lobes; such type of hemorrhage was most common in the parietal (34.1%) and occipital (29.3%) regions, less common in the frontal (17.1%), temporal (14.6%) regions and cerebellar (4.9%) in our patients.

Although the localization of the hematomas in CAA usually excludes HTN as an etiological factor,

studies dealing with HTN-related ICH demonstrated that the cause of lobar ICH was HTN in 20% to 48% of the patients (Kase, 1991).

Neau *et al*. (1997) reported that 11 of 17 patients (64.7%) with primary bleeding in lobar areas had HTN related ICH. Broderick *et al*.(1993) showed that the prevalence of HTN in ICH and that the contribution of HTN to ICH was similar in patients with lobar hemorrhages compared with deep hemipheric, cerebellar, and pontine hemorrhage. We found no difference in the prevalence of HTN between the different sites of ICH: the HTN-related hemorrhage showed lobar distribution in 42.9% of cases and affected the basal ganglia and thalamic region in 40.5%, and cerebellum in 16.7% of cases in our series. Lobar hemorrhage in HTN was most common in the occipital (19.0%) and the parietal (14.3%) regions, less common in the frontal and temporal (4.8%) regions.

Cerebellar hemorrhage in CAA-related ICH occurs only rarely, with less than 10 cases reported previously (Cuny *et al.*, 1996). In our series 2 patients (4.9%), who also had a history of HTN, had cerebellar hemorrhages in CAA.

In HTN, however, 16.7% had cerebellar hemorrhage in our series. Rupture of microaneurysms due to HTN in the deep small penetrating vessels may account for the location of the hemorrhage in the thalamus, putamen, or cerebellum. It is difficult, if not entirely impossible, to distinguish CAA-related ICH from HTN-related ICH on CT and MRI scans in cerebellar hemorrhages.

Previous reports pointed out that lobulated or irregularly shaped hematoma was a characteristic feature of amyloid angiopathy (Wakai *et al.*, 1992; Minakawa *et al.*, 1995; Itoh and Yamada, 1997). Our own data showed that 17 of 41 cases (41.5%) in CAA-related ICH had such features on CT or MRI whereas only 5 of 42 cases (11.9%) in HTN-related ICH had such statistically different features. Although there was a greater frequency of round and irregular shaped hematomas in HTN-related ICH, this was not a statistically significant difference.

There was a significant hematoma size difference between CAA-related ICH and HTN-related ICH. While the large and medium sized hematomas (≥30 ml) accounted for 85.3% of hematomas in CAA-related ICH, only 14.6% of such hemorrhages were small. In HTN-related ICH, however, the large and medium sized hematomas (≥30 ml) account for 59.5% while the small hematomas account for 40.5% of hemorrhages.

In the search for an explanation of these interesting findings, one might speculate that the amyloid protein which accumulates within the adventitia and tunica media replacing the contractile elements and producing a fragile and brittle wall may render such vessels prone to rupture. It is conceivable that replacement of such contractile elements interferes with their vasoconstrictory properties and, in case of sudden rupture, may lead to larger hematomas. Such deficient vasoconstriction might also contribute to possible secondary enlargement of the hematoma in CAA-related hemorrhage leading to a potentially lobulated shape.

In addition, it had been suggested that the endothelium of amyloid-laden vessels may be functionally deficient (Thomas *et al*., 1996). Such a deficient endothelium might fail to inhibit circulating plasmin and plasminogen activator, possibly leading to larger hematomas and, once again, to a potentially lobulated appearance.

Furthermore the replacement of collagen by amyloid in the subendothelial layer might interfere with platelet adhesion and aggregation because the amyloid accumulations might bind prothrombin as well as factors XII and IX, and interfering with their role in the hemostatic cascade (Ramsay *et al*., 1990). Contrary to such considerations, however, it has been argued that although the internal elastic lamina is frequently fragmented and split in patients with CAA, the endothelium itself is usually spared except in the most severe cases.

Several recent studies demonstrated that A4/β-protein accumulates in the affected cerebral vessel walls and damaged vascular smooth muscle and/or vascular endothelial cells, suggesting that it inhibits vascular contraction and/or platelet adhesion (Thomas *et al*., 1996; Behl *et al*., 1994).

Although we cannot prove that such particular circumstances apply to our own series there is

reasonable evidence to substantiate an explanation why CAA-related ICH tended to be larger in size in comparison with HTN-related ICH and have a distinct lobulated shape and appearance.

SAH was frequently found in CAA-related ICH. Hemorrhage due to CAA is most commonly the lobar type and therefore easily ruptures into the subarachnoid space. On CT acute CAA-related ICH can have the characteristic appearance of a hematoma at the cortex-white matter junction with extension of blood into the subarachnoid, subdural, and intraventricular spaces. SAH which was initially seen on CT and MRI scans, and which was later confirmed during surgery is the most reliable indicator that the hemorrhage is caused by CAA. Other reports confirmed that secondary SAH from lobar hemorrhage was frequent in CAA-related ICH and that secondary SAH was almost constantly found on pathological examination. Yamada *et al.* (1993) investigated the relationship between SAH and CAA to clarify the contribution of CAA to SAH in elderly individuals. Eleven of 23 patients (47.8%) with secondary SAH developed from CAA-related ICH. In these cases ICH developed in the following location: 5 in the temporal lobe, 3 in the frontal lobe, 2 in the occipital lobe, and 2 in the cerebellum. Six of 23 patients (26.1%) had secondary SAH developed from HTN.

In our series we found 26 of 41 cases (63.4%) with SAH on CT and MRI scans in CAA-related ICH. The locations of ICH were: 12 in the parietal lobe, 8 in the occipital lobe, 3 in the temporal and the frontal lobe respectively. Only 11 of 42 (26.2%) HTN-related ICH cases were SAH observed. Corresponding ICH were found as follows: 3 in the occipital lobe, 2 in the parietal lobe and cerebellum, respectively, 1 in the temporal and the frontal lobe respectively, another 2 in the basal ganglionic and thalamic regions. The frequency of SAH in CAA-related ICH was higher than that in HTN-related ICH ($P<0.05$). There were reports suggesting that secondary SAH was frequent in CAA-related ICH. The finding that CAA-related ICH was commonly associated with secondary SAH can be explained by the superficial location of CAA-related vascular pathology with fibrinoid necrosis and microaneurysm formations in the cortical arteries (Yamada *et al*., 1993). A high resolution CT scan with thin slice sections can detect the cortical involvement and SAH.

A CAA-related ICH can also disrupt the white matter and rupture through the ependyma into the ventricular system. Izumihara *et al*.(1999) reported that 5 of 37 patients (13.5%) with CAA-related ICH had IVH and were defined as intraventricular rupture from lobar hemorrhage. In our series, 10 of 41 cases (24.4%) in CAA-related ICH were accompanied by secondary IVH defined as intraventricular rupture from lobar hemorrhage; almost the same frequency was found in HTN-related ICH (25.6%). The associated ICH was located as follows: 6 in the parietal lobe, 2 in the temporal lobe, 1 in the frontal and the occipital lobe respectively. In contrast all ICH with IVH in the hypertensive patients' group originated from either basal ganglionic/thalamic hemorrhage and or cerebellar hemorrhage.

This feature has so far not been mentioned in the literature and we would suggest that IVH rupture from lobar hemorrhage may be a characteristic feature of CAA-related ICH. It appears plausible to argue that because hematomas in CAA-related ICH are larger there is a very similar frequency of IVH in both groups although this cannot be definitely proven.

CONCLUSION

Based on evidence in the literature and based on our own series, we have confirmed established characteristic finding of ICH caused by CAA and established new ones. The typical features of CAA-related ICH included CAA-related ICH increased with age, lobar hemorrhage, affecting mainly the lobar superficial areas, lobulated shaped hematoma, rupture into the subarachnoid space and the secondary IVH from lobar hemorrhage, multiplicity of hemorrhage, bilaterality, and repeated episodes. To some extent, these features may contribute to distinguish CAA from HTN related ICH.

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