CASE REPORT

J Korean Neurosurg Soc 39 : 447-450, 2006

Multiple Recurrent Cerebral Hemorrhages Related to Cerebral Amyloid Angiopathy with Arterial Hypertension

Jae-Hyun Jung, M.D., Dong-Ah Shin, M.D., Tae-Sik Gong, M.D., Chang-Young Kwon, M.D.

Department of Neurosurgery, Presbyterian Medical Center, Jeonju, Korea

Cerebral amyloid angiopathy(CAA) is characterized by the deposition of amyloid β-protein in the walls of small to medium-sized arteries of the leptomeninges and cerebral cortex. While often asymptomatic, CAA can develop into intracerebral hemorrhage facilitated by arterial hypertension. We report the case of a 52-year-old man with CAA and arterial hypertension who developed recurrent cerebral hemorrhages on three different occasions and in multiple non-overlapping loci over a period of nine years. Based on our findings, we recommend brain biopsies for all patients undergoing evacuation of multiple recurrence or atypical pattern intracerebral hemorrhages.

KEY WORDS : Cerebral amyloid angiopathy · Recurrent cerebral hemorrhages.

Introduction

Cerebral amyloid angiopathy(CAA) is increasingly recognized as a cause of lobar intracerebral hemorrhage(ICH) in normotensive, elderly individuals[15]. CAA is characterized by the deposition of amyloid β-protein in the walls of small to medium-sized arteries of the leptomeninges and the cerebral cortex[8,14]. The incidence of CAA increases with age, but the process usually remains asymptomatic[15]. However, a minority of patients develop single or multiple CAA-related hemorrhages, known to be facilitated by arterial hypertension[11].

Here, the authors describe a 52-year-old man with CAA and arterial hypertension who developed recurrent cerebral hemorrhages on three different occasions, in multiple non-overlapping loci over a nine-year period.

Case Report

A 52-year-old, right-handed man with a history of arterial hypertension presented to our hospital as an emergency. He had suddenly developed left-sided hemiparesis one hour before admission. The motor grade of his left arm was measured as grade 2, and that of his left leg as grade 4. At the time of admission, he was mentally alert. He was a non-smoker, was not a heavy drinker, and had no liver disease. Previously, he had had three intracerebral hemorrhage(ICH) attacks over a period of nine years. With the first attack, he developed slurred speech and right-sided hemiparesis. A brain computed tomography(CT) scan showed a left basal ganglia hematoma with no mass effect (Fig. 1A), and arterial hypertension was initially observed. Seven years after his initial symptomatic cerebral hemorrhage, he developed partial seizure and right-sided quadrantanopsia. A brain CT scan at that time demonstrated a new left occipital and a right frontal lobe hematoma (Fig. 1B). One year ago, the patient developed an ICH at the right parietal lobe (Fig. 1C) which presented with a partial seizure. No operation was performed for any of the three ICH attacks, and his symptoms improved conservatively.

At the time of this admission, his blood pressure was 150/100mmHg and he was known to have had arterial hypertension for nine years. It was presumed that his arterial hypertension had not been well controlled, as he reported to have frequently skipped his medication. Spontaneous international normalized ratio(INR) values, platelet counts, prothrombin time, and partial thromboplastin time were all normal. For his known arterial hypertension, he had been prescribed 50mg

• Received : December 7, 2005 • Accepted : February 3, 2006
• Address for reprints : Dong-Ah Shin, M.D., Department of Neurosurgery, Presbyterian Medical Center, Jungwhasan-dong, Wansan-gu, Jeonju 560-750, Korea Tel : +82-63-230-8266, Fax : +82-63-285-9573, E-mail : cistern@hanmail.net

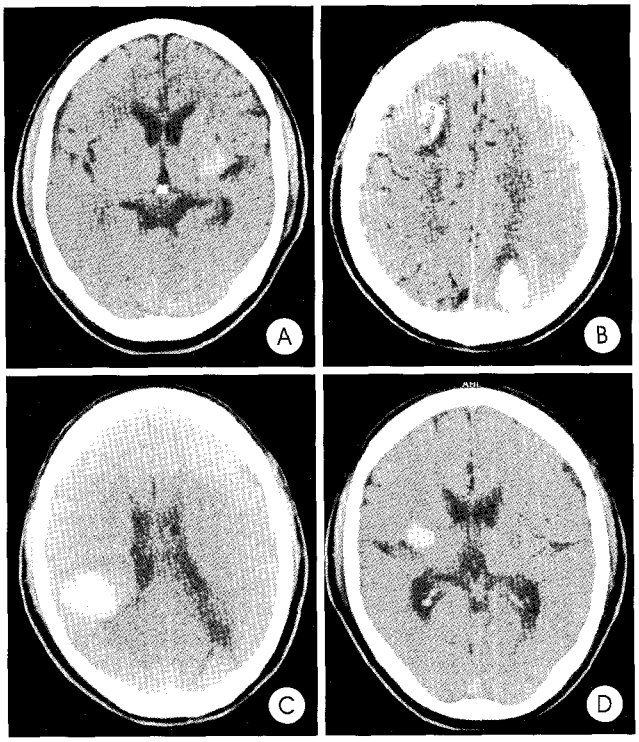

Fig. 1. A : Computed tomography showing left basal ganglia hemorrhage with symptoms of slumed speech and hemiparesis 9 years before last event. B : Left occipital and right frontal lobar hemorrhage developed 7 years after initial hemorrhage. C : Computed tomography showing the third event of hemorrhage in the right parietal lobe 8 years after initial event. D : The last hemorrhage event in the right basal ganglia.

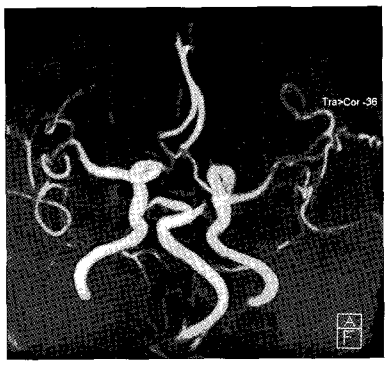

Fig. 2. Magnetic resonance angiography shows no gross vascular abnormality.

atenolol (Tenormin, Hyundai Pharmaceuticals, Seoul, South Korea) once daily, and, to control seizures, with 300mg valproate sodium (Orfil R-etard, Bukwang Pharmaceuticals, Seoul, South Korea) three times daily. A brain CT scan performed on the latest admission showed a right basal ganglia hematoma with a moderate mass effect (Fig. 1D). Magnetic resonance angiography ruled out other vascular malformations (Fig. 2). After three days in the hospital, the patient's left arm became more paralytic. A second brain CT scan showed the hematoma slightly increased in size. We performed stereotactic ICH catheter insertion through Kocher's point.

Because the development of four recurrent cerebral hemorrhages in multiple non-overlapping loci is very rare, we decided to perform a biopsy of the frontal cortex and the subcortical white matter simultaneously, through the same tract. The brain

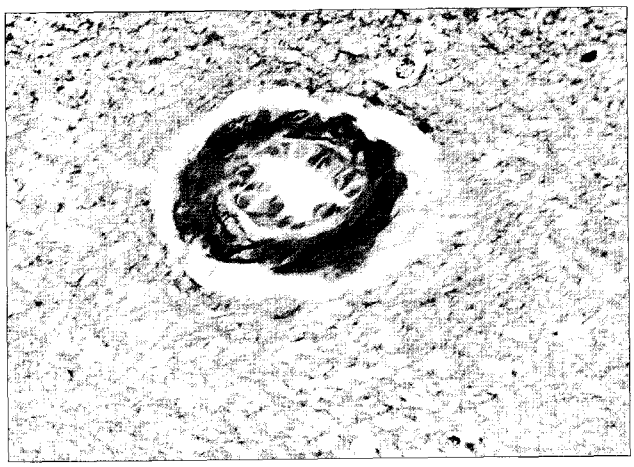

Fig. 3. The thickened small artery is densely stained with Congo-red (X100).

tissue that spontaneously came out due to increased intracranial pressure was regarded as tissue from the basal ganglia and was also included in the histologic examination. The brain tissues were stored in 10% formalin and given to a pathologist for analysis. The samples were embedded in paraffin and thin, 6-μm sections were cut and stained with Congo red. Congo red staining of these vessels revealed the presence of CAA (Fig. 3). We graded the severity of CAA by scoring severity in single arteries, a method proposed by Vonsattel et al[17]. A score of 2 was given to this patient because although the entire wall was replaced by amyloid, the architecture of the vessel was preserved. There was no evidence of metastatic disease or hemorrhagic infarction. After 3 months, the patient had somewhat recovered, but still experienced weakness in his left arm.

Discussion

Known risk factors of ICH are arterial hypertension, blood disorders, antiplatelet or anticoagulant medications, alcoholism, male gender, liver disease, brain tumors, trauma, and old age[1]. It has been estimated that sporadic cerebral amyloid angiopathy accounts for about 4~10% of all cases of primary ICH[6]. Nevertheless, CAA has frequently been overlooked in clinical studies as a risk factor for ICH[6]. Lee et al., who first reported CAA in South Korea, emphasized that the occurrence of nontraumatic normotensive spontaneous primary cerebral hemorrhage in the elderly indicates the existence of CAA[6]. CAA is characterized by the deposition of amyloid β-protein in small to medium-sized arteries of the leptomeninges and the cerebral cortex[8,14]. Leblanc et al. suggested that the replacement of contractile elements with noncontractile amyloid interferes with vasoconstriction, the first phenomenon in vascular trauma and the initial phase of hemostasis, thus promoting the development of ICHs[5].

The patient had developed recurrent cerebral hemorrhages

three times in non-overlapping, multiple loci over the last nine years. This case posed a diagnostic challenge for two reasons. First, to have ICH recur three times over nine years is quite rare. Second, the patterns of recurrence were atypical for both hypertensive and CAA-related ICHs. These two points will be discussed in order.

In South Korea, the rate of ICH recurrence has been reported to range between 2.7% and 11.7%[2,7,10], and the interval between hemorrhages has reportedly ranged from 13.1 to 22.3 months[2,7,10]. In one series, 0.9% of cases had two occurrences of rebleeding[10]. On the other hand, 25~40% of individuals with CAA-related hemorrhage experience recurrence, with the highest risk in the first year. Reported cases of four repeated hemorrhages are very rare. In fact, only Tyler et al. have reported such a case, in which a 63-year-old patient survived four repeated cerebral hemorrhages[13]. In our case, the patient also survived four ICHs, and because this is very rare in both hypertensive and CAA-related ICHs, we decided to perform a brain biopsy to pathologically confirm this diagnosis.

With respect to the relationship between the site of an initial ICH and that of a recurrent ICH, two main patterns have been reported : ganglionic-ganglionic and lobar-lobar. The gagnlionic-ganglionic pattern likely results from hypertension because most hypertensive ICHs occur in the basal ganglia, whereas the lobar-lobar pattern probably results from amyloid angiopathy. Specific localization of amyloid-laden vessels in the cortex and leptomeninges, excluding the deep gray nuclei and cerebellum, makes CAA more prone to lead to lobar ICH than deep ICH[3,4,16,17]. The ICHs of our patient showed a ganglionic-lobar-lobar-ganglionic pattern. The first and the fourth ICH events were deep ganglionic bleeding, and these were caused exclusively by CAA. Such a feature is typical of hypertensive ICH, although not all CAA is associated with ganglionic bleeding. Invariably, hematoma due to CAA is based in the cerebral cortex, but sometimes extends to the subcortical white matter. The cortical hematoma ruptures through the pial membrane, producing a focal subarachnoid hemorrhage. In severe cases, the arachnoid membrane ruptures and an associated arterialized subdural hematoma can add to the mass effect of the intracerebral clot. Similarly, the hematoma can extend to the white matter and rupture into the ventricular system. Notwithstanding these conditions, solitary deep ganglionic bleeding due to CAA is still rare.

In spite of pathological confirmation of CAA in our patient, the two deep ICHs call into question the diagnosis of CAA. There may be doubt as to whether there is any relationship between two typical hypertensive ICHs and CAA. Usually, two independent pathologic mechanisms do not involve the same disease simultaneously. The uncontrolled arterial hypertension in our patient may have exacerbated the tendency for CAA-related hemorrhages. Ritter et al. reported that there is a weak association between CAA and deep ICH[11]. They also reported that the absolute number of patients with proven CAA was small for the deep ICH subgroup and in controls, and they did not find CAA in any specimens from the basal ganglia[11]. It is possible that CAA might lead to impaired autoregulation and impairment of the blood-brain barrier[9,12], and thereby facilitate the transmission of potentially harmful blood pressure peaks to the small arteries of the basal ganglia and the brain stem[11]. CAA may therefore increase the risk of deep ICH via indirect effects[11]. The authors regard this case as further evidence of the above hypothesis, and suggest that the patient's two deep ICHs developed by this mechanism. After excluding other causes of hemorrhage, the patient's clinical presentation combined with results of the cerebral biopsy strongly supports the diagnosis of CAA.

Conclusion

We suggest that the presence of CAA should be taken into account when diagnosing and treating recurrent ICH even if hypertension is present. And suggest a dominant role of CAA in the pathogenesis of hemorrhage in such cases. We recommend brain biopsies in all patients undergoing evacuation of ICHs of multiple recurrence or atypical pattern.

References

1. Ariesen MJ, Claus SP, Rinkel GJ, Algra A : Risk factors for intracerebral hemorrhage in the general population : a systematic review. **Stroke 34 :** 2060-2065, 2003
2. Bae HG, Jeong DS, Doh JW, Lee KS, Yun IG : Recurrent intracerebral hemorrhage. **J Korean Neurosug Soc 28 :** 335-339, 1999
3. Gilbert JJ, Vinters HV : Cerebral amyloid angiopathy : incidence and complications in the aging brain. I. Cerebral hemorrhage. **Stroke 14 :** 915-923, 1983
4. Itoh Y, Yamada M, Hayakawa M, Otomo E, Miyatake T : Cerebral amyloid angiopathy : a significant cause of cerebellar as well as lobar cerebral hemorrhage in the elderly. **J Neurol Sci 116 :** 135-141, 1993
5. Leblanc R, Carpenter S, Stewart J, Pokrupa R : Subacute enlarging cerebral hematoma from amyloid angiopathy : case report. **Neurosurgery 36 :** 403-406, 1995
6. Lee HS, Park IS, Whang SH, Paek SH, Kim ES, Jung JM, et al : A case of cerebral amyloid angiopathy-related intracerebral hemorrhage. **J Korean Neurosug Soc 27 :** 387-391, 1998
7. Lee KS, Bae HG, Yun IG : Recurrent intracerebral hemorrhage due to hypertension. **Neurosurgery 26 :** 586-590, 1990
8. Maruyama K, Kametani F, Ikeda S, Ishihara T, Yanagisawa N : Characterization of amyloid fibril protein from a case of cerebral amyloid angiopathy showing immunohistochemical reactivity for both beta protein and cystatin C. **Neurosci Lett 144 :** 38-42, 1992
9. Pantoni L, Garcia JH : Pathogenesis of leukoaraiosis : a review. **Stroke 28 :** 652-659, 1997
10. Park SI, Kang DG, Kim SC : Recurrent hypertensive intracerebral hemorrhage. **J Korean Neurosug Soc 22 :** 1213-1219, 1993
11. Ritter MA, Droste DW, Hegedus K, Szepesi R, Nabavi DG, Csiba L, et al : Role of cerebral amyloid angiopathy in intracerebral hemorrhage in hypertensive patients. **Neurology 64 :** 1233-1237, 2005
12. Tian J, Shi J, Bailey K, Mann DM : Relationships between arteriosclerosis, cerebral amyloid angiopathy and myelin loss from cerebral cortical white matter in Alzheimer's disease. **Neuropathol Appl Neurobiol 30 :**

46-56, 2004
13. Tyler KL, Poletti CE, Heros RC : Cerebral amyloid angiopathy with multiple intracerebral hemorrhages. Case report. **J Neurosurg 57** : 286-289, 1982
14. Van Broeckhoven C, Haan J, Bakker E, Hardy JA, Van Hul W, Wehnert A, et al : Amyloid beta protein precursor gene and hereditary cerebral hemorrhage with amyloidosis (Dutch). **Science 248** : 1120-1122, 1990
15. Vinters HV : Cerebral amyloid angiopathy. A critical review. **Stroke 18** : 311-324, 1987
16. Vinters HV, Gilbert JJ : Cerebral amyloid angiopathy : incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. **Stroke 14** : 924-928, 1983
17. Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr : Cerebral amyloid angiopathy without and with cerebral hemorrhages : a comparative histological study. **Ann Neurol 30** : 637-649, 1991

Commentary

This paper documents a case of multiple and recurrent intracerebral hemorrhages(ICHs) developed from hypertension and cerebral amyloid angiopathy(CAA). In view of the 4 times recurrence of ICHs locating in other different areas and the young age compared with the age range occurring CAA, it is an interesting case. CAA-related lobar hemorrhage usually affects elderly normotensive individuals. The hematoma involves the corticosubcortical region, extends from the cortex to the subarachnoid space and is lobular in shape. In this report, whereas the first and fourth ICHs occurred in deep ganglionic portions as a typical hypertensive ICH, the second and third ICHs were lobar types suggesting CAA, which was pathologically confirmed. Thus, this paper can make an argument for the role of CAA in the pathogenesis of deep ICH or the role of hypertension in the recurrence of CAA-related lobar hemorrhage.

CAA may lead to impair autoregulation and blood-brain barrier, and the transmission of the harmful blood pressure peaks to the small arteries of basal ganglia and brain stem may be facilitated. CAA may therefore increase the risk of deep ICH via indirect effect[2]. Izumihara et al.[1] reported risk factors for the recurrence and extension of ICH in 40 surgically treated patients with lobar hemorrhage diagnosed histologically as being related to CAA. They concluded that hypertension was the only significant clinical factor influencing the recurrence of CAA-related lobar hemorrhage and a strict control of blood pressure may prevent the recurrence of CAA-related lobar hemorrhage[1]. Even though role of CAA or hypertension for recurrent ICHs is still controversial, either of them or both may facilitate in the recurrence of ICHs because both CAA and hypertension are related with aging process.

References

1. Izumihara A, Suzuki M, Ishihara T : Recurrence and extension of lobar hemorrhage related to cerebral amyloid angiopathy : multivariate analysis of clinical risk factors. **Surg Neurol 64** : 160-164, 2005
2. Ritter MA, Droste DW, Hegedüs K, Szepesi R, Nabavi DG, Csiba L, et al : Role of cerebral amyloid angiopathy in intracerebral hemorrhage in hypertensive patients. **Neurology 64** : 1233-1237, 2005

Hack-Gun Bae, M.D.
Soonchunhyang University Chonan Hospital