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

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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. 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. The incidence of CAA increases with age, but the process usually remains asymptomatic. However, a minority of patients develop single or multiple CAA-related hemorrhages, known to be facilitated by arterial hypertension.

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 asymptomatic cerebral hemorrhage, he developed partial seizure and right-sided quadrantanopia. 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 150/100 mmHg 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...
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. It has been estimated that sporadic cerebral amyloid angiopathy accounts for about 4–10% of all cases of primary ICH. Nevertheless, CAA has frequently been overlooked in clinical studies as a risk factor for ICH. 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. CAA is characterized by the deposition of amyloid β-protein in small to medium-sized arteries of the leptomeninges and the cerebral cortex. 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 ICH.

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%\(^{6,16}\), and the interval between hemorrhages has reportedly ranged from 13.1 to 22.3 months\(^{2,4,10}\). In one series, 0.9% of cases had two occurrences of rebleeding\(^{16}\). 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\(^{18}\). 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 ganglionic-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\(^{14,16,17}\). The ICHs of our patient showed a ganglionic-lobar-ganglionic-lobar 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\(^{10}\). 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\(^{10}\). It is possible that CAA might lead to impaired autoregulation and impairment of the blood-brain barrier\(^{9,10}\), 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**

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 corticostriatocortical 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. Izumihiara et al. 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. 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

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