CASE REPORT

New microbleed after blood–brain barrier leakage in intracerebral haemorrhage

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SUMMARY

Cerebral microbleeds are increasingly recognised as biomarkers of small vessel disease. Several preclinical and clinical studies have suggested that chronic disruption of the blood–brain barrier is one of the mechanisms for the development of cerebral microbleeds.

A 51-year-old man experienced two left parieto-occipital lobar intracerebral haemorrhages (ICHs) in the timespan of 2 years. Multiple microbleeds surrounding the two haemorrhages were found on MRI, but not at location distant from the haemorrhages. Ten months after the last haemorrhage, an MRI demonstrated a right occipital focus of contrast enhancement. Twenty months after the last ICH, a new cerebral microbleed had developed exactly at the location of the earlier contrast enhancement.

This case demonstrates that blood–brain barrier disruption may be an important factor preceding the development of cerebral microbleeds.

BACKGROUND

Cerebral microbleeds (CMBs) are small areas of blood product deposition in the brain, seen as signal voids on MR sequences susceptible to the paramagnetic effects of blood products, such as T2*-weighted gradient echo. Since the initial report by Fazekas *et al*,¹ they have received increasing attention as biomarkers of cerebral small vessel disease. They are most prevalent in patients with recurrent intracerebral haemorrhage (ICH)² but also observed in patients with ischaemic stroke,² cognitive decline³ and normal ageing.⁴ Two of the main underlying disease processes leading to the development of CMBs are cerebral amyloid angiopathy (CAA) and hypertensive vasculopathy.⁵

Disturbance of the blood–brain barrier has previously been implicated as one of the mechanisms involved in the development of CMBs.^{6,7} Indeed, CMBs have been demonstrated in other conditions with blood–brain barrier disruption apart from small vessel disease, including infective endocarditis⁸ and radiation therapy.⁹ A recent study showed that after acute lacunar stroke, the presence of biomarkers for blood–brain barrier disruption (S100B and RAGE) in plasma was associated with an increasing number of CMBs.¹⁰

CASE PRESENTATION

A 51-year-old Caucasian right-handed male with a medical history of diabetes mellitus type 2 and hypercholesterolaemia and a documented normal

blood pressure presented with acute headache and a right homonymous quadrantanopia. He never smoked, had no history of alcohol or drug abuse and the family history was unremarkable. CT imaging revealed a haemorrhage in the left parieto-occipital region (*figure 1A*). On MRI 1 (Philips Healthcare), no underlying cause was identified other than some indication of small vessel disease consisting of mild white matter lesions, most prominent adjacent to the posterior horn of the left ventricle (Fazekas 1). Two years later, the patient reported fatigue, abnormal coordination of his right arm, and difficulties with calculations and reading. A CT scan showed a recurrent ICH in the same region, cranial to the tissue defect from the first haematoma (*figure 1B*). CT angiography and a digital subtraction angiography performed at that time revealed no underlying macrovascular cause. Eight months after the second ICH, the patient was referred to our centre. At neurological examination, the patient displayed difficulties performing arithmetic tasks. Further examination was unremarkable.

After the first ICH, MRI (MRI 1, *figure 2A*) with a T2* sequence demonstrated numerous round signal voids in the area of the haematoma, consistent with CMBs and no signs indicative of a tumour or cavernous malformation. A subsequent MRI 6 months after the second ICH (MRI 2, *figure 2B*, Siemens) showed an increase in the number of signal voids in the area of the two haematomas, consistent with the deposition of new blood products. No additional microbleeds were seen at locations distant from the two haemorrhages.

Ten months after the second ICH, we performed a high-field 7 Tesla MR scan (MRI 3, Philips Healthcare). As we had not been able to establish a cause for the ICHs in this patient, we used

Figure 1 (A) First ICH and (B) second ICH on CT. ICH, intracerebral haemorrhage.

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Figure 2 MRI 1: 1T T2* gradient echo 4 months after the first ICH (A), MRI 2: 1T T2* gradient echo 6 months after the second ICH (B). MRI 3: 7T three-dimensional fluid-attenuated inversion recovery (10 month after second ICH) before contrast (C) and after contrast (D): small focus of enhancement (inset). MRI 3: 7T T2* gradient echo: no microbleed in the right occipital lobe (E). MRI 4: 3T susceptibility-weighted imaging 10 months later showing new microbleed in the same location as previous enhancement (inset) (F). ICH, intracerebral haemorrhage.

high-field MRI to detect CMBs or superficial siderosis that would support a diagnosis of CAA with maximum sensitivity. This MRI included a dual echo T2*-weighted sequence. We reconstructed minimum intensity projections of the first and

second echo. In addition, we included precontrast and postcontrast 3D fluid-attenuated inversion recovery (FLAIR) images to investigate signs of blood–brain barrier leakage as part of our scientific interest in ICH. We found no additional CMBs (figure 2E) or superficial siderosis. On the 3D FLAIR acquired 10 min after administration of gadolinium contrast, we found one sulcal focus of contrast enhancement in the right occipital region (figure 2C,D). In this region, there were no signs of a parenchymal lesion at that time. In addition, several foci of enhancement were observed in the left parieto-occipital region, adjacent to the haemorrhage. We performed a 3 Tesla MR scan (MRI 4, Philips Healthcare) 20 months after the second ICH to determine whether new CMBs had developed over time that would lend support to the diagnosis of CAA. On this examination, a CMB had developed in the right occipital region, exactly at the location where we had previously observed the contrast enhancement (figure 2F). No gadolinium was administered during this examination.

Figure 3 summarises the timeline of clinical symptoms and CT and MR scans.

DIFFERENTIAL DIAGNOSIS

At the time of referral, a macrovascular cause and a tumour had already been excluded. The clinical symptoms and course had not been suggestive of vasculitis or endocarditis, and the family history was negative for genetic causes of ICH or its associated symptoms (HCHWA-D, CADASIL, COL4A1). Hypertension-related vasculopathy was unlikely because of the lobar location of the ICHs and the documented absence of high blood pressure. An overview of the differential diagnosis of ICH is listed in box.

Despite the relatively young age of the patient at the time of his first haemorrhage, we concluded that the most likely cause of his disease was CAA, based on the absence of hypertension, the lobar parieto-occipital location of the haemorrhages, the occurrence of a new occipital CMB in the contralateral hemisphere over time and the absence of macrovascular causes. No other causes of microangiopathy were identified. As he was below 55 years of age, he did not fulfil the modified Boston criteria for probable CAA.¹¹ Because of the lack of therapeutic consequences, we did not perform a biopsy to confirm the diagnosis.

OUTCOME AND FOLLOW-UP

The patient remained clinically stable at follow-up 33 months after the last ICH.

DISCUSSION

We observed the emergence of a new cerebral microbleed in the exact same area where contrast enhancement was found 10 months earlier in a patient with a history of two lobar ICHs in the contralateral hemisphere.

Figure 3 A timeline illustrating the timing of the 2 ICHs and the 4 MRIs. CMB, cerebral microbleed; ICH, intracerebral haemorrhage.

Box Differential diagnosis of non-traumatic intracerebral haemorrhage**Spontaneous intracerebral haemorrhage**

- ▶ Hypertension-related small vessel disease
- ▶ Cerebral amyloid angiopathy

Secondary intracerebral haemorrhage

- ▶ Arteriovenous malformation
- ▶ Aneurysm
- ▶ Cerebral venous sinus thrombosis
- ▶ Cerebral cavernous malformation
- ▶ Dural arteriovenous fistula
- ▶ Vasculitis
- ▶ Moyamoya disease
- ▶ Intracranial dissection
- ▶ Coagulopathy
- ▶ Haemorrhagic transformation of ischaemic stroke
- ▶ Neoplasm
- ▶ Drug abuse
- ▶ Genetic: HCHWA-D, CADASIL, COL4A1

Gadolinium contrast enhancement is a known biomarker of blood–brain barrier disruption and has previously been used to demonstrate blood–brain barrier disruption in patients with ICH in the acute phase,¹² Alzheimer's disease,¹³ lacunar stroke and white matter lesions.¹⁴ Studies of spontaneously hypertensive stroke-prone rats have suggested that blood–brain barrier hyperpermeability precedes haemorrhage and occurs early in the pathological cascade of cerebral small vessel disease.^{6,15} Stasis of erythrocytes in the microvasculature may be the first histologically observable sign of the pathological cascade that involves blood–brain barrier damage and subsequently microthrombosis, microbleeds, macrobleeds and infarcts.^{6,16}

In a study of 19 patients with CAA, two patients showed blood–brain barrier leakage of gadolinium.¹⁷ In both patients, there were severe white matter changes and one of the patients had presented with a posterior reversible encephalopathic syndrome 10 months earlier.¹⁷ In the same study, the authors demonstrated that in isolated rat brain microvessels amyloid- β_{40} decreased the expression of tight junction proteins and increased expression of matrix metalloproteinase 2 and 9, both indicating increased blood–brain barrier permeability.¹⁷ Moreover, permeability was increased in brain microvessels from transgenic human amyloid precursor protein-overexpressing mice compared with microvessels from wild-type controls.¹⁷

Learning points

- ▶ New microbleeds in patients with small vessel disease-related intracerebral haemorrhage may be preceded by blood–brain barrier disruption.
- ▶ Restoration of the blood–brain barrier should be evaluated as a potential novel treatment target to prevent haemorrhage in patients at risk of intracerebral haemorrhage caused by small vessel disease, including cerebral amyloid angiopathy.
- ▶ Relatively young age does not preclude the clinical phenotype of cerebral amyloid angiopathy.

Our case is the first to demonstrate in vivo that asymptomatic focal gadolinium leakage is followed by emergence of a microbleed at exactly the location of the gadolinium leakage several months later. It also illustrates that patients with a likely diagnosis of CAA may experience their first ICH before the age of 55 years—the minimum age to fulfil the modified Boston criteria for CAA.

Our case observation lends further support to the hypothesis that the blood–brain barrier disruption is associated with small vessel diseases that cause ICH. Treatment aimed at prevention or restoring of blood–brain leakage may be a potential treatment target to prevent haemorrhage in patients with ICH due to small vessel disease such as CAA and hypertensive vasculopathy.

Contributors CJMK conceived the case report. All authors contributed to the analysis and interpretation of the case. KMN wrote the first draft of the manuscript. CJMK and JH critically revised the manuscripts intellectual content. All authors read and approved the final version for publication.

Competing interests None declared.

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